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Vaccines for preventing rotavirus diarrhoea: vaccines in use (Review)

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[Intervention Review]

Vaccines for preventing rotavirus diarrhoea: vaccines in use

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ABSTRACT

Background

Rotavirus is a common cause of diarrhoea, diarrhoea-related hospital admissions, and diarrhoea-related deaths worldwide. Rotavirus vaccines prequalified by the World Health Organization (WHO) include Rotarix (GlaxoSmithKline), RotaTeq (Merck), and, more recently, Rotasiil (Serum Institute of India Ltd.), and Rotavac (Bharat Biotech Ltd.).

Objectives

To evaluate rotavirus vaccines prequalified by the WHO for their efficacy and safety in children.

Search methods

On 30 November 2020, we searched PubMed, the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (published in the Cochrane Library), Embase, LILACS, Science Citation Index Expanded, Social Sciences Citation Index, Conference Proceedings Citation Index-Science, Conference Proceedings Citation Index-Social Science & Humanities. We also searched the WHO ICTRP, ClinicalTrials.gov, clinical trial reports from manufacturers' websites, and reference lists of included studies, and relevant systematic reviews.

Selection criteria

We selected randomized controlled trials (RCTs) conducted in children that compared rotavirus vaccines prequalified for use by the WHO with either placebo or no intervention.

Data collection and analysis

Two authors independently assessed trial eligibility and assessed risk of bias. One author extracted data and a second author cross-checked them. We combined dichotomous data using the risk ratio (RR) and 95% confidence interval (CI). We stratified the analyses by under-five country mortality rate and used GRADE to evaluate evidence certainty.

Main results

Sixty trials met the inclusion criteria and enrolled a total of 228,233 participants. Thirty-six trials (119,114 participants) assessed Rotarix, 15 trials RotaTeq (88,934 participants), five trials Rotasiil (11,753 participants), and four trials Rotavac (8432 participants).

Rotarix

Infants vaccinated and followed up for the first year of life

In low-mortality countries, Rotarix prevented 93% of severe rotavirus diarrhoea cases (14,976 participants, 4 trials; high-certainty evidence), and 52% of severe all-cause diarrhoea cases (3874 participants, 1 trial; moderate-certainty evidence).

In medium-mortality countries, Rotarix prevented 79% of severe rotavirus diarrhoea cases (31,671 participants, 4 trials; high-certainty evidence), and 36% of severe all-cause diarrhoea cases (26,479 participants, 2 trials; high-certainty evidence).

In high-mortality countries, Rotarix prevented 58% of severe rotavirus diarrhoea cases (15,882 participants, 4 trials; high-certainty evidence), and 27% of severe all-cause diarrhoea cases (5639 participants, 2 trials; high-certainty evidence).

Children vaccinated and followed up for two years

In low-mortality countries, Rotarix prevented 90% of severe rotavirus diarrhoea cases (18,145 participants, 6 trials; high-certainty evidence), and 51% of severe all-cause diarrhoea episodes (6269 participants, 2 trials; moderate-certainty evidence).

In medium-mortality countries, Rotarix prevented 77% of severe rotavirus diarrhoea cases (28,834 participants, 3 trials; high-certainty evidence), and 26% of severe all-cause diarrhoea cases (23,317 participants, 2 trials; moderate-certainty evidence).

In high-mortality countries, Rotarix prevented 35% of severe rotavirus diarrhoea cases (13,768 participants, 2 trials; moderate-certainty evidence), and 17% of severe all-cause diarrhoea cases (2764 participants, 1 trial; high-certainty evidence).

RotaTeq

Infants vaccinated and followed up for the first year of life

In low-mortality countries, RotaTeq prevented 97% of severe rotavirus diarrhoea cases (5442 participants, 2 trials; high-certainty evidence).

In medium-mortality countries, RotaTeq prevented 79% of severe rotavirus diarrhoea cases (3863 participants, 1 trial; low-certainty evidence).

In high-mortality countries, RotaTeq prevented 57% of severe rotavirus diarrhoea cases (6775 participants, 2 trials; high-certainty evidence), but there is probably little or no difference between vaccine and placebo for severe all-cause diarrhoea (1 trial, 4085 participants; moderate-certainty evidence).

Children vaccinated and followed up for two years

In low-mortality countries, RotaTeq prevented 96% of severe rotavirus diarrhoea cases (5442 participants, 2 trials; high-certainty evidence).

In medium-mortality countries, RotaTeq prevented 79% of severe rotavirus diarrhoea cases (3863 participants, 1 trial; low-certainty evidence).

In high-mortality countries, RotaTeq prevented 44% of severe rotavirus diarrhoea cases (6744 participants, 2 trials; high-certainty evidence), and 15% of severe all-cause diarrhoea cases (5977 participants, 2 trials; high-certainty evidence).

We did not identify RotaTeq studies reporting on severe all-cause diarrhoea in low- or medium-mortality countries.

Rotasiil

Rotasiil has not been assessed in any RCT in countries with low or medium child mortality.

Infants vaccinated and followed up for the first year of life

In high-mortality countries, Rotasiil prevented 48% of severe rotavirus diarrhoea cases (11,008 participants, 2 trials; high-certainty evidence), and resulted in little to no difference in severe all-cause diarrhoea cases (11,008 participants, 2 trials; high-certainty evidence).

Children vaccinated and followed up for two years

In high-mortality countries, Rotasiil prevented 44% of severe rotavirus diarrhoea cases (11,008 participants, 2 trials; high-certainty evidence), and resulted in little to no difference in severe all-cause diarrhoea cases (11,008 participants, 2 trials; high-certainty evidence).

Rotavac

Rotavac has not been assessed in any RCT in countries with low or medium child mortality.

Infants vaccinated and followed up for the first year of life

In high-mortality countries, Rotavac prevented 57% of severe rotavirus diarrhoea cases (6799 participants, 1 trial; moderate-certainty evidence), and 16% of severe all-cause diarrhoea cases (6799 participants, 1 trial; moderate-certainty evidence).

Children vaccinated and followed up for two years

In high-mortality countries, Rotavac prevented 54% of severe rotavirus diarrhoea cases (6541 participants, 1 trial; moderate-certainty evidence); no Rotavac studies have reported on severe all-cause diarrhoea at two-years follow-up.

Safety

No increased risk of serious adverse events (SAEs) was detected with Rotarix (103,714 participants, 31 trials; high-certainty evidence), RotaTeq (82,502 participants, 14 trials; moderate to high-certainty evidence), Rotasiil (11,646 participants, 3 trials; high-certainty evidence), or Rotavac (8210 participants, 3 trials; moderate-certainty evidence).

Deaths were infrequent and the analysis had insufficient evidence to show an effect on all-cause mortality. Intussusception was rare.

Authors' conclusions

Rotarix, RotaTeq, Rotasiil, and Rotavac prevent episodes of rotavirus diarrhoea. The relative effect estimate is smaller in high-mortality than in low-mortality countries, but more episodes are prevented in high-mortality settings as the baseline risk is higher. In high-mortality countries some results suggest lower efficacy in the second year. We found no increased risk of serious adverse events, including intussusception, from any of the prequalified rotavirus vaccines.

PLAIN LANGUAGE SUMMARY

Are rotavirus vaccines safe and effective in preventing rotavirus diarrhoea in infants and children?

What is the aim of this review?

The aim of this Cochrane Review was to find out if rotavirus vaccines are effective in preventing diarrhoea and deaths in infants and young children. We also aimed to find out if the rotavirus vaccines are safe. We collected and analysed all relevant studies to answer these questions.

Key messages

Rotarix, RotaTeq, Rotasiil, and Rotavac prevent the large majority of episodes of rotavirus diarrhoea during the first year of a child's life, when diarrhoea is most dangerous, with a slightly lower efficacy during the second year. We found no increased risk of serious adverse events (moderate- to high-certainty evidence) including intussusception (where the bowel telescopes on itself, and can cause obstruction).

What was studied in the review?

Rotavirus infection is a common cause of diarrhoea in infants and young children, and can cause mild illness, hospitalization, and death. Since 2009, the World Health Organization (WHO) has recommended that a rotavirus vaccine be included in all national infant and child immunization programmes. To date, 96 countries have followed this recommendation. In the years before infants and children started receiving rotavirus vaccine, rotavirus infection resulted in about half a million deaths a year in children aged under five years, mainly in low- and middle-income countries.

In this review, we included randomized controlled trials in infants and young children that evaluated rotavirus vaccination with Rotarix (GlaxoSmithKline) or RotaTeq (Merck). These vaccines have been evaluated in several large trials and are approved for use in many countries. We also included trials that evaluated Rotavac (Bharat Biotech Ltd.) and Rotasiil (Serum Institute of India Ltd.), rotavirus vaccines which are currently used in India only. The rotavirus vaccines were compared with placebo or with no vaccine. The included studies did not allow comparisons between the different rotavirus vaccines.

What are the main results of the review?

We found 60 relevant studies with a total of 228,233 participants. The trials took place in several locations worldwide. The vaccines tested were Rotarix (36 trials with 119,114 participants), RotaTeq (15 trials with 88,934 participants), Rotasiil (five trials with 11,753 participants), and Rotavac (four trials with 8432 participants). Fifty-six studies were funded or co-funded by vaccine manufacturers, while four were independent of manufacturer funding.

In the first two years of life, we found that rotavirus vaccines prevent more than 90% of severe cases of rotavirus diarrhoea in countries with low child mortality rates, more than 75% in countries with medium child mortality rates, and 35% to 58% in countries with high child mortality rates.

Rotavirus vaccines probably prevent more than 50% of severe cases of diarrhoea from all causes (such as any viral infection, bacterial infection, or parasitic infection) in countries with low child mortality rates, 26% to 36% in countries with medium child mortality rates, and none to 27% in countries with high child mortality rates.

The evidence for countries with low and medium child mortality rates comes from studies of Rotarix and RotaTeq vaccines; these two vaccines have been evaluated in all settings. Rotasiil and Rotavac vaccines have only been assessed in countries with high child mortality rates.

We found little or no difference in the number of serious adverse events between those receiving rotavirus vaccines compared with placebo or with no vaccine.

Rotavirus vaccines may make little to no difference to the number of deaths or to intussusception cases, compared with placebo or no vaccine, but the certainty of the evidence was limited for these rare outcomes.

How up-to-date is this review?

We searched for studies that had been published up to 30 November 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Rotarix compared with placebo for preventing rotavirus diarrhoea in low-mortality countries

Patient or population: children
Setting: low-mortality countries
Intervention: Rotarix, 2 doses
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Rotarix				
Severe cases of rotavirus diarrhoea Follow-up: up to 1 year	**13 per 1000**	**1 per 1000** (0 to 2)	**RR 0.07** (0.03 to 0.18)	14,976 (4 RCTs)	⊕⊕⊕⊕ **high**	Rotarix reduces severe rotavirus diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of rotavirus diarrhoea Follow-up: up to 2 years	**29 per 1000**	**3 per 1000** (2 to 4)	**RR 0.10** (0.07 to 0.14)	18,145 (6 RCTs)	⊕⊕⊕⊕ **high**	Rotarix reduces severe rotavirus diarrhoea compared with placebo at up to two years follow-up.
Severe cases of all-cause diarrhoea Follow-up: up to 1 year	**94 per 1000**	**45 per 1000** (35 to 58)	**RR 0.48** (0.37 to 0.61)	3874 (1 RCT)	⊕⊕⊕⊖ **moderate**[a] *due to reporting bias*	Rotarix probably reduces severe all-cause diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of all-cause diarrhoea Follow-up: up to 2 years	**84 per 1000**	**41 per 1000** (34 to 51)	**RR 0.49** (0.40 to 0.60)	6269 (2 RCTs)	⊕⊕⊕⊖ **moderate**[b] *due to reporting bias*	Rotarix probably reduces severe all-cause diarrhoea compared with placebo at up to two years follow-up. One additional study reported on *episodes* of children with severe all-cause diarrhoea (rate ratio 0.70, 95% CI 0.56 to 0.86; n = 10,519); these data could not be pooled with the studies reporting on number of *cases.*
All-cause death Follow-up: 2 months to 2 years	**0 per 1000**	**0 per 1000** (0 to 1)	**RR 0.71** (0.17 to 2.88)	20,361 (10 RCTs)	⊕⊕⊖⊖ **low**[c]	Rotarix may result in little to no difference in all-cause death compared with placebo.

					due to serious imprecision	
All serious adverse events Follow-up: 2 months to 2 years	**44 per 1000**	**39 per 1000** (32 to 48)	**RR 0.89** (0.72 to 1.10)	18,971 (12 RCTs)	⊕⊕⊕⊕ **high**	Rotarix results in little to no difference in serious adverse events compared with placebo.
Serious adverse events: intussusception Follow-up: 2 months to 2 years	**1 per 1000**	**1 per 1000** (0 to 3)	**RR 1.42** (0.52 to 3.87)	20,773 (10 RCTs)	⊕⊕⊖⊖ **low**[d] *due to serious imprecision*	Rotarix may result in little to no difference in intussusception compared with placebo.

*The basis for the **assumed risk** is the control group risk across studies included in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT**: randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded by one level for risk of selective reporting bias. Only one of the four studies reporting on severe rotavirus diarrhoea provided data for this outcome.
[b]Downgraded by one level for risk of selective reporting bias. Only three of the six studies reporting on severe rotavirus diarrhoea provided data for this outcome.
[c]Downgraded by two levels for serious imprecision. These trials were not powered to detect an effect on mortality.
[d]Downgraded by two levels for serious imprecision: very few events with wide 95% CIs that included no effect.

Summary of findings 2. Rotarix compared with placebo for preventing rotavirus diarrhoea in medium-mortality countries

Patient or population: children
Setting: medium-mortality countries
Intervention: Rotarix, 2 doses
Comparison: placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Rotarix**				

Severe cases of rotavirus diarrhoea Follow-up: up to 1 year	**13 per 1000**	**3 per 1000** (2 to 4)	**RR 0.21** (0.16 to 0.29)	31,671 (4 RCTs)	⊕⊕⊕⊕ **high**	Rotarix reduces severe rotavirus diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of rotavirus diarrhoea Follow-up: up to 2 years	**25 per 1000**	**6 per 1000** (4 to 7)	**RR 0.23** (0.17 to 0.29)	23,834 (3 RCTs)	⊕⊕⊕⊕ **high**	Rotarix reduces severe rotavirus diarrhoea compared with placebo at up to two years follow-up.
Severe cases of all-cause diarrhoea Follow-up: up to 1 year	**38 per 1000**	**25 per 1000** (20 to 30)	**RR 0.64** (0.52 to 0.79)	26,479 (2 RCTs)	⊕⊕⊕⊕ **high**	Rotarix reduces severe all-cause diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of all-cause diarrhoea Follow-up: up to 2 years	**78 per 1000**	**58 per 1000** (39 to 85)	**RR 0.74** (0.50 to 1.09)	23,317 (2 RCTs)	⊕⊕⊖⊖ **low**[a,b] *due to serious inconsistency*	Rotarix may reduce severe all-cause diarrhoea compared with placebo at up to two years follow-up. Serious inconsistency (I^2 = 92%) in the pooled data: RIX Li 2014-CHN: RR 0.91 (0.75 to 1.09), n = 3148; RIX Ruiz-Palac 06-LA/EU: RR 0.61 (0.55 to 0.69), n = 20,169.
All-cause death Follow-up: 2 months to 2 years	**1 per 1000**	**2 per 1000** (1 to 3)	**RR 1.27** (0.89 to 1.81)	77,043 (9 RCTs)	⊕⊕⊕⊖ **moderate**[c] *due to imprecision*	Rotarix probably results in little to no difference in all-cause death compared with placebo.
All serious adverse events Follow-up: 2 months to 2 years	**45 per 1000**	**38 per 1000** (34 to 43)	**RR 0.85** (0.76 to 0.95)	77,069 (9 RCTs)	⊕⊕⊕⊕ **high**	Rotarix reduces serious adverse events compared with placebo.
Serious adverse events: intussusception Follow-up: 2 months to 2 years	**1 per 1000**	**0 per 1000** (0 to 1)	**RR 0.72** (0.39 to 1.32)	75,540 (6 RCTs)	⊕⊕⊖⊖ **low**[d] *due to imprecision*	Rotarix may result in little to no difference in intussusception compared with placebo.

*The basis for the **assumed risk** is the control group risk across studies included in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

[a] Downgraded by two levels for serious inconsistency in the pooled data: $I^2 = 92\%$.
[b]Although the 95% CI included both no effect and appreciable benefit, we did not downgrade for imprecision since it arose due to inconsistency between two precise estimates which was accounted for by downgrading for inconsistency.
[c]Downgraded by one level for imprecision. The 95% CI was wide and included both no effect and appreciable harm.
[d]Downgraded by two levels for serious imprecision: very few events with wide 95% CIs that included no effect.

Summary of findings 3. Rotarix compared with placebo for preventing rotavirus diarrhoea in high-mortality countries

Patient or population: children
Settings: high-mortality countries
Intervention: Rotarix, 2 doses
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no intervention	Rotarix				
Severe cases of rotavirus diarrhoea Follow-up: up to 1 year	**40 per 1000**	**17 per 1000** (11 to 25)	**RR 0.42** (0.28 to 0.61)	15,822** (5 comparisons from 4 RCTs)	⊕⊕⊕⊕ **high**[a]	Rotarix reduces severe rotavirus diarrhoea compared with placebo or no intervention at up to one-year follow-up. Sensitivity analysis excluding the cluster-RCT (RIX Zaman 2017-BGD) that contributed data to this outcome showed no important change in the effect estimate or 95% CI (RR 0.37, 95% CI 0.23 to 0.60, n = 6114, 3 RCTs with 4 comparisons).
Severe cases of rotavirus diarrhoea Follow-up: up to 2 years	**43 per 1000**	**28 per 1000** (22 to 35)	**RR 0.65** (0.51 to 0.83)	13,768** (3 comparisons from 2 RCTs)	⊕⊕⊕⊖ **moderate**[c] *due to risk of bias*	Rotarix probably reduces severe rotavirus diarrhoea compared with placebo or no intervention at up to two years follow-up. Sensitivity analysis excluding the cluster-RCT (RIX Zaman 2017-BGD) that contributed data to this outcome showed no important change in the effect estimate or 95% CI (RR 0.58, 95% CI 0.42 to 0.79, n = 2764, 1 RCT with 2 comparisons).

Severe cases of all-cause diarrhoea Follow-up: up to 1 year	**176 per 1000**	**129 per 1000** (99 to 167)	**RR 0.73** (0.56 to 0.95)	5639 (3 comparisons from 2 RCTs)	⊕⊕⊕⊕ **high**[d]	Rotarix reduces severe all-cause diarrhoea compared with placebo or no intervention at up to one-year follow-up.
Severe cases of all-cause diarrhoea Follow-up: up to 2 years	**233 per 1000**	**194 per 1000** (168 to 224)	**RR 0.83** (0.72 to 0.96)	2764 (2 comparisons from 1 RCT)	⊕⊕⊕⊕ **high**	Rotarix reduces severe all-cause diarrhoea compared with placebo at up to two years follow-up.
All-cause death Follow-up: 2 months to 2 years	**20 per 1000**	**18 per 1000** (13 to 25)	**RR 0.88** (0.63 to 1.21)	8374 (11 RCTs)	⊕⊕⊕⊖ **moderate**[e] *due to imprecision*	Rotarix probably results in little to no difference in all-cause death compared with placebo or no intervention.
All serious adverse events Follow-up: 2 months to 2 years	**92 per 1000**	**83 per 1000** (71 to 96)	**RR 0.90** (0.77 to 1.05)	7674 (10 RCTs)	⊕⊕⊕⊕ **high**	Rotarix results in little to no difference in serious adverse events compared with placebo or no intervention.
Serious adverse events: intussusception Follow-up: 2 months to 2 years	**not estimable**, no events in control group, 1 event in intervention group	**not estimable**, no events in control group, 1 event in intervention group	**RR 1.49** (0.06 to 36.63)	17,068** (5 RCTs)	⊕⊕⊖⊖ **low**[f] *due to serious imprecision*	Rotarix may result in little to no difference in intussusception compared with placebo or no intervention. Sensitivity analysis excluding the cluster-RCT (RIX Zaman 2017-BGD) that contributed data to this outcome showed no change in the effect estimate or 95% CI.

*The basis for the **assumed risk** is the control group risk across studies included in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**Number of participants in this table shows the true number of participants for this outcome; the number of events and the number of participants in the analysis has been adjusted for the included cluster trial RIX Zaman 2017-BGD using a design effect of 2.53.
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]We did not downgrade for inconsistency as the heterogeneity observed in the pooled data (I^2 = 52%) was due to within-study heterogeneity (RIX Madhi 2010-AF results split by country).
[b]Downgraded by two levels for serious imprecision; wide 95% CIs that included both appreciable benefit and appreciable harm.
[c]Downgraded by one for risk of bias: the largest trial contributing data (RIX Zaman 2017-BGD) was a cluster-RCT where participants, carers and investigators were aware of treatment allocation.
[d]We did not downgrade for inconsistency as the heterogeneity observed in the pooled data (I^2 = 75%) was due to within-study heterogeneity (RIX Madhi 2010-AF results split by country).
[e]Downgraded by one level for imprecision; wide 95% CIs that included both appreciable benefit and no effect.
[f]Downgraded by two levels for serious imprecision: very few events with wide 95% CIs that included no effect.

Summary of findings 4. RotaTeq compared with placebo for preventing rotavirus diarrhoea in low-mortality countries

Patient or population: children
Settings: low-mortality countries
Intervention: RotaTeq, 3 doses
Comparison: placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Certainty** of the evidence (GRADE)	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**RotaTeq**				
Severe cases of rotavirus diarrhoea Follow-up: up to 1 year	**23 per 1000**	**1 per 1000** (0 to 3)	**RR 0.03** (0.01 to 0.11)	7688 (5 RCTs)	⊕⊕⊕⊕ **high**	RotaTeq reduces severe rotavirus diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of rotavirus diarrhoea Follow-up: up to 2 years	**32 per 1000**	**1 per 1000** (0 to 4)	**RR 0.04** (0.01 to 0.11)	5442 (2 RCTs)	⊕⊕⊕⊕ **high**	RotaTeq reduces severe rotavirus diarrhoea compared with placebo at up to two years follow-up.
Severe all-cause diarrhoea Follow-up: up to 1 year	-	-	-	-	-	We found no studies that reported on this outcome in this setting.
Severe all-cause diarrhoea Follow-up: up to 2 years	-	-	-	-	-	We found no studies that reported on this outcome in this setting.
All-cause death Follow-up: 2 months to 2 years	**1 per 1000**	**1 per 1000** (0 to 1)	**RR 1.24** (0.69 to 2.22)	72,654 (6 RCTs)	⊕⊕⊖⊖ **low**[a]	RotaTeq may result in little to no difference in all-cause death compared with placebo.

					due to serious imprecision	
All serious adverse events Follow-up: 2 months to 2 years	**26 per 1000**	**24 per 1000** (22 to 26)	**RR 0.92** (0.84 to 1.01)	70,690 (5 RCTs)	⊕⊕⊕⊕ **high**	RotaTeq results in little to no difference in serious adverse events compared with placebo.
Serious adverse events: intussusception Follow-up: 2 months to 2 years	**1 per 1000**	**0 per 1000** (0 to 1)	**RR 0.69** (0.35 to 1.38)	73,925 (9 RCTs)	⊕⊕⊖⊖ **low**[b] *due to serious imprecision*	RotaTeq may result in little to no difference in intussusception compared with placebo.

*The basis for the **assumed risk** is the control group risk across studies included in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded by two levels for serious imprecision. These trials were not powered to detect an effect on mortality.
[b]Downgraded by two levels for serious imprecision: very few events with wide 95% CIs that included no effect.

Summary of findings 5. RotaTeq compared with placebo for preventing rotavirus diarrhoea in medium-mortality countries

Patient or population: children
Settings: medium-mortality countries
Intervention: RotaTeq, 3 doses
Comparison: placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Certainty** of the evidence (GRADE)	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**RotaTeq**				
Severe cases of rotavirus diarrhoea	-	-	-	-	-	We found no studies that reported on this outcome in this setting.

Follow-up: up to 1 year						
Severe cases of rotavirus diarrhoea Follow-up: up to 2 years	**27 per 1000**	**6 per 1000** (3 to 11)	**RR 0.21** (0.11 to 0.41)	3863 (1 RCT)	⊕⊕⊖⊖ **low**[a,b] *due to risk of bias and indirectness*	RotaTeq may reduce severe rotavirus diarrhoea compared with placebo at up to two years follow-up.
Severe all-cause diarrhoea Follow-up: up to 1 year	-	-	-	-	-	We found no studies that reported on this outcome in this setting.
Severe all-cause diarrhoea Follow-up: up to 2 years	-	-	-	-	-	We found no studies that reported on this outcome in this setting.
All-cause death Follow-up: 2 months to 2 years	**0 per 1000**	**0 per 1000** (0 to 4)	**RR 0.33** (0.01 to 8.18)	4088 (2 RCTs)	⊕⊕⊖⊖ **very low**[a,c,d] *due to risk of bias, indirectness, and serious imprecision*	The evidence is very uncertain about the effect of RotaTeq on all-cause death.
All serious adverse events Follow-up: 2 months to 2 years	**58 per 1000**	**38 per 1000** (8 to 185)	**RR 0.66** (0.14 to 3.17)	4082 (2 RCTs)	⊕⊖⊖⊖ **very low**[a,e] *due to risk of bias and imprecision*	The evidence is very uncertain about the effect of RotaTeq on serious adverse events.
Serious adverse events: intussusception Follow-up: 2 months to 2 years	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 5.01** (0.24 to 104.29)	4082 (2 RCTs)	⊕⊖⊖⊖ **very low**[a,e] *due to risk of bias and serious imprecision*	The evidence is very uncertain about the effect of RotaTeq on intussusception.

*The basis for the **assumed risk** is the control group risk across studies included in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded by one level for risk of bias; unclear risk of selection bias.
[b]Downgraded by one level for indirectness; single study carried out in China; difficult to apply results to any medium-mortality settings.

[c]Downgraded by one level for indirectness; two studies carried out in China; difficult to apply results to any medium-mortality settings.
[d]Downgraded by two levels for serious imprecision. These trials were not powered to detect an effect on mortality.
[e]Downgraded by two levels for serious imprecision: very few events with wide 95% CIs that included no effect.

Summary of findings 6. RotaTeq compared with placebo for preventing rotavirus diarrhoea in high-mortality countries

Patient or population: children
Settings: high-mortality countries
Intervention: RotaTeq, 3 doses
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	RotaTeq				
Severe cases of rotavirus diarrhoea Follow-up: up to 1 year	**28 per 1000**	**12 per 1000** (8 to 18)	**RR 0.43** (0.29 to 0.64)	6775 (2 RCTs)	⊕⊕⊕⊕ **high**	RotaTeq reduces severe rotavirus diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of rotavirus diarrhoea Follow-up: up to 2 years	**59 per 1000**	**33 per 1000** (27 to 51)	**RR 0.56** (0.41 to 0.77)	6744 (2 RCTs)	⊕⊕⊕⊕ **high**	RotaTeq reduces severe rotavirus diarrhoea compared with placebo at up to two years follow-up.
Severe cases of all-cause diarrhoea Follow-up: up to 1 year	**77 per 1000**	**62 per 1000** (45 to 85)	**RR 0.80** (0.58 to 1.11)	4085 (1 RCT)	⊕⊕⊕⊖ **moderate**[a] *due to imprecision*	RotaTeq probably results in little to no difference in severe all-cause diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of all-cause diarrhoea Follow-up: up to 2 years	**130 per 1000**	**110 per 1000** (96 to 128)	**RR 0.85** (0.74 to 0.99)	5977 (2 RCTs)	⊕⊕⊕⊕ **high**	RotaTeq slightly reduces severe all-cause diarrhoea compared with placebo at up to two years follow-up.
All-cause death Follow-up: 2 months to 2 years	**23 per 1000**	**21 per 1000** (16 to 28)	**RR 0.91** (0.68 to 1.23)	7706 (3 RCTs)	⊕⊕⊕⊖ **moderate**[a] *due to imprecision*	RotaTeq probably results in little to no difference in all-cause death compared with placebo.

All serious adverse events Follow-up: 2 months to 2 years	**19 per 1000**	**19 per 1000** (14 to 26)	**RR 0.99** (0.72 to 1.36)	7730 (4 RCTs)	⊕⊕⊕⊖ **moderate**[b] *due to imprecision*	RotaTeq probably results in little to no difference in serious adverse events compared with placebo.
Serious adverse events: intussusception Follow-up: 2 months to 2 years	**0 per 1000**	**0 per 1000** (0 to 2)	**RR 0.33** (0.01 to 8.16)	7488 (2 RCTs)	⊕⊕⊖⊖ **low**[c] *due to serious imprecision*	RotaTeq may result in little to no difference in intussusception compared with placebo.

*The basis for the **assumed risk** is the control group risk across studies included in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded by one level for imprecision. The 95% CI included both no effect and appreciable benefit.
[b]Downgraded by one level for imprecision. The 95% CI included both no effect and appreciable harm.
[c]Downgraded by two levels for serious imprecision: very few events with wide 95% CIs that included no effect.

Summary of findings 7. Rotasiil compared with placebo for preventing rotavirus diarrhoea in high-mortality countries

Patient or population: children

Settings: high-mortality countries (Niger, India)

Intervention: Rotasiil, 3 doses

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Rotasiil				

Severe cases of rotavirus diarrhoea follow-up: up to 1 year	**45 per 1000**	**23 per 1000** (15 to 36)	**RR 0.52** (0.33 to 0.81)	11,008 (2 RCTs)	⊕⊕⊕⊕ **high**[a]	Rotasiil reduces severe rotavirus diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of rotavirus diarrhoea follow-up: up to 2 years	**76 per 1000**	**43 per 1000** (32 to 56)	**RR 0.56** (0.42 to 0.74)	11,008 (2 RCTs)	⊕⊕⊕⊕ **high**[a]	Rotasiil reduces severe rotavirus diarrhoea compared with placebo at up to two years follow-up.
Severe cases of all-cause diarrhoea follow-up: up to 1 year	**145 per 1000**	**133 per 1000** (121 to 146)	**RR 0.92** (0.84 to 1.01)	11,008 (2 RCTs)	⊕⊕⊕⊕ **high**	Rotasiil results in little to no difference in severe all-cause diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of all-cause diarrhoea follow-up: up to 2 years	**239 per 1000**	**225 per 1000** (211 to 242)	**RR 0.94** (0.88 to 1.01)	11,008 (2 RCTs)	⊕⊕⊕⊕ **high**	Rotasiil results in little to no difference in severe all-cause diarrhoea compared with placebo at up to two years follow-up.
All-cause death follow-up: up to 2 years	**11 per 1000**	**13 per 1000** (9 to 18)	**RR 1.14** (0.82 to 1.59)	11,586 (2 RCTs)	⊕⊕⊕⊖ **moderate**[b] *due to imprecision*	Rotasiil probably results in little to no difference in all-cause death compared with placebo at up to two years follow-up.
All serious adverse events follow-up: up to 2 years	**264 per 1000**	**258 per 1000** (242 to 274)	**RR 0.98** (0.92 to 1.04)	11,646 (3 RCTs)	⊕⊕⊕⊕ **high**	Rotasiil results in little to no difference in serious adverse events compared with placebo at up to two years follow-up. In addition: SIIL Zade 2014-INDb reported that "Two SAEs (urinary tract infections and septicaemia) unrelated to study vaccines were reported and both recovered uneventfully". No SAEs were reported among 18 infants and 18 toddlers in SIIL Zade 2014-INDa.
Serious adverse events: intussusception follow-up: up to 2 years	**1 per 1000**	**1 per 1000** (0 to 3)	**RR 0.98** (0.35 to 2.74)	11,586 (2 RCTs)	⊕⊕⊖⊖ **low**[c] *due to serious imprecision*	Rotasiil may result in little to no difference in intussusception compared with placebo at up to two years follow-up.

*The basis for the **assumed risk** is the control group risk across studies included in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[a]There was unexplained statistical heterogeneity in this analysis (I^2 > 50%), however, we did not downgrade for inconsistency since all estimates were in the same direction showing appreciable benefit.
[b]Downgraded by one level for imprecision: wide 95% CIs that included no effect as well as appreciable harm.
[c]Downgraded by two levels for serious imprecision: very few events with wide 95% CIs that included no effect.

Summary of findings 8. Rotavac compared with placebo for preventing rotavirus diarrhoea in high-mortality countries

Patient or population: children

Settings: one high-mortality country (India)

Intervention: Rotavac, 3 doses

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Rotavac				
Severe cases of rotavirus diarrhoea follow-up: up to 1 year	**31 per 1000**	**13 per 1000** (9 to 19)	**RR 0.43** (0.30 to 0.60)	6799 (1 study)	⊕⊕⊕⊖ **moderate**[a] *due to indirectness*	Rotavac probably reduces severe rotavirus diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of rotavirus diarrhoea follow-up: up to 2 years	**47 per 1000**	**21 per 1000** (16 to 28)	**RR 0.46** (0.35 to 0.60)	6541 (1 study)	⊕⊕⊕⊖ **moderate**[a] *due to indirectness*	Rotavac probably reduces severe rotavirus diarrhoea compared with placebo at up to two years follow-up.

Severe cases of all-cause diarrhoea follow-up: up to 1 year	**93 per 1000**	**78 per 1000** (66 to 91)	**RR 0.84** (0.71 to 0.98)	6799 (1 study)	⊕⊕⊕⊖ **moderate**[a] *due to indirectness*	Rotavac probably slightly reduces severe all-cause diarrhoea compared with placebo at up to one-year follow-up.
Severe cases of all-cause diarrhoea follow-up: up to 2 years	-	-	-	-	-	We found no studies that reported on this outcome in this setting.
All-cause death follow-up: up to 2 years	**7 per 1000**	**6 per 1000** (3 to 11)	**RR 0.88** (0.50 to 1.56)	8155 (2 studies)	⊕⊖⊖⊖ **very low**[b,c] *due to indirectness and serious imprecision*	The evidence is very uncertain about the effect of Rotavac on all-cause death.
All serious adverse events follow-up: up to 2 years	**204 per 1000**	**189 per 1000** (173 to 208)	**RR 0.93** (0.85 to 1.02)	8210 (3 studies)	⊕⊕⊕⊖ **moderate**[b] *due to indirectness*	Rotavac probably results in little to no difference in serious adverse events compared with placebo.
Serious adverse events: intussusception follow-up: up to 2 years	**1 per 1000**	**1 per 1000** (0 to 5)	**RR 1.33** (0.35 to 5.02)	8582 (4 studies)	⊕⊖⊖⊖ **very low**[b,d] *due to indirectness and serious imprecision*	No events were reported in three of the four studies. The evidence is very uncertain about the effect of Rotavac on intussusception.

*The basis for the **assumed risk** is the control group risk across studies included in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[a]Downgraded by one level for indirectness; single trial conducted in India, so generalization to any high-mortality country is difficult.
[b]Downgraded by one level for indirectness. All trials were conducted in India, so generalization to any high-mortality country is difficult.
[c]Downgraded by two levels for serious imprecision. These trials were not powered to detect an effect on mortality.
[d]Downgraded by two levels for serious imprecision: very few events with wide 95% CIs that included no effect.

BACKGROUND

Description of the condition

The global impact of rotavirus infection

Rotavirus is the leading known cause of severe gastroenteritis in infants and young children worldwide (Parashar 2006a; Vesikari 1997; WHO 2021b). While nearly every child experiences at least one rotavirus infection in early childhood regardless of setting, most rotavirus-associated deaths occur in children in low- and middle-income countries, particularly in sub-Saharan Africa and in the Indian subcontinent. Prior to the rollout of rotavirus vaccination, rotavirus caused 37% of diarrhoeal deaths (~ 450,000 deaths worldwide in 2008) in children younger than five years. Five countries accounted for more than half of all deaths, and 22% of deaths attributable to rotavirus infection occurred in India (Tate 2012). In high-income countries, where deaths due to rotavirus are rare, rotavirus accounted for 40% to 50% of hospital admissions due to diarrhoeal disease in the pre-rotavirus vaccine period (Linhares 2008; Parashar 2006a; Tate 2012).

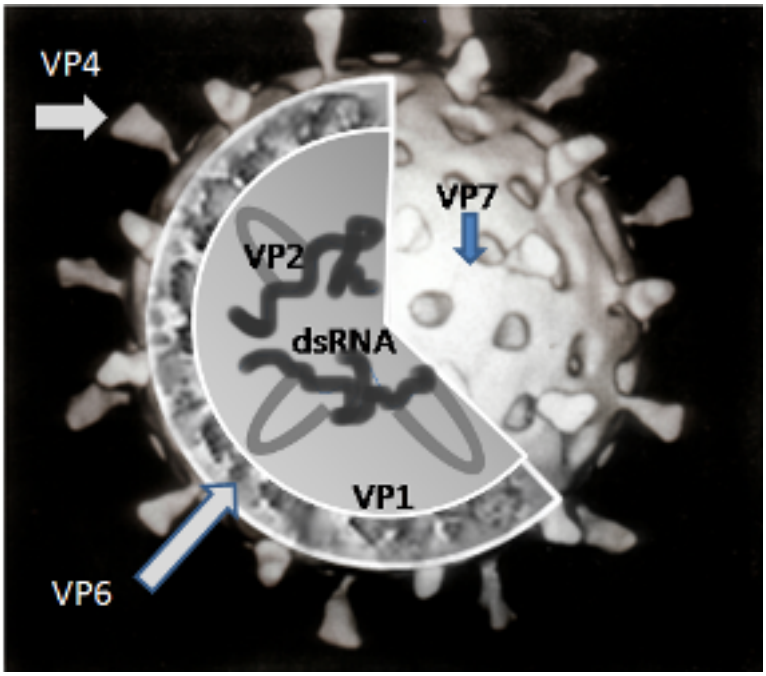
Epidemiology of rotavirus infection

Rotavirus is transmitted primarily via the faecal-oral route, with symptoms typically developing one to two days following infection. Rotavirus infection occurs throughout life, and successive rotavirus infections occur during infancy and early childhood. The first rotavirus infection typically results in the most severe disease outcome; subsequent rotavirus infections are associated with milder disease or may be asymptomatic. However, differences in the age of first infection and number of infections required to acquire protection from symptomatic disease vary from one population to another. Rotavirus diarrhoea is particularly associated with severe outcomes between the ages of three and 35 months (Parashar 2006b), with a peak incidence of all episodes occurring between six and 24 months (CDC-ASIP 1999; Linhares 2008). The peak incidence of severe rotavirus disease occurs earlier in high-mortality countries than in low-mortality countries; an estimated 43% of all rotavirus hospitalizations in children aged under five occur by eight months of age in Africa compared with 27% in Europe (Crawford 2017; Sanderson 2011). Typically, infants in high-mortality countries experience a greater number of symptomatic episodes (Gladstone 2011; Velázquez 1996). In temperate countries, rotavirus infections display marked seasonality, with distinct peaks during the winter months and few infections identified outside this period. In contrast, rotavirus infections tend to occur year-round in many tropical countries, which nevertheless often display peaks of more intense activity and within-country variation in seasonal patterns (Patel 2013)

Rotavirus classification

Rotaviruses are double-stranded (ds) ribonucleic acid (RNA) viruses: genus *Rotavirus*, family *Reoviridae*. Each of the 11 dsRNA segments, contained within the core of a triple-layered viral particle, encodes one or more viral proteins. *Rotavirus A,* which causes most human disease, is genetically diverse in each of its 11 genome segments (called genotypes), and a nucleotide sequence-based, complete genome classification system is used. Because of their importance in protective immunity, the outer capsid proteins VP7 and VP4 have been most extensively investigated. Species A rotaviruses are classified into G and P genotypes, based on the sequence diversity of the RNA segments encoding VP7 and VP4, respectively; 32 G genotypes and 47 P genotypes have been described (Crawford 2017) (see Figure 1 for details). Rotavirus vaccines are designed to protect against disease caused by the most prevalent strain types; globally, G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] and G12 in combination with P[6] or P[8] account for over 90% of the genotypes that infect humans (Bányai 2012).

Figure 1. A simplified diagram of the location of rotavirus structural proteins (source: Graham Cohn, Wikipedia (public domain image)): Rotaviruses are segmented, double-stranded RNA viruses. The mature, triple-layered virus particle comprises a core (which contains the viral genome), a middle layer (comprised of viral protein (VP)6, and an outer layer (comprised of VP7 and VP4) as shown in the figure. VP6 defines rotavirus group, and most rotaviruses that infect humans are of group A. The two outer capsid proteins independently induce neutralizing antibodies: VP7, a glycoprotein, defines G-serotype; and the protease-sensitive VP4 protein defines P-serotype. G-serotype determined by serological methods correlates precisely with G-genotype obtained through molecular assays, whereas there is an imperfect correlation of P-serotype and P-genotype; P-genotype is thus included in square brackets.



Description of the intervention

Vaccines approved for use

This review evaluates four vaccines that are listed as prequalified by the WHO (WHO 2021a). They include a monovalent rotavirus vaccine (Rotarix, GlaxoSmithKline Biologicals) and a pentavalent rotavirus vaccine (RotaTeq, Merck & Co., Inc.), which have been evaluated in multiple large trials across several continents and are in routine use in many countries. Also included is a further monovalent vaccine (Rotavac, Bharat Biotech Ltd.), and a further pentavalent vaccine (BRV-PV, Rotasiil, Serum Institute of India Ltd.) which are licensed and used in India. As of April 2020, 107 countries have introduced rotavirus vaccines into their immunization programmes (ROTA Council 2021).

Rotarix is an oral, live-attenuated, human rotavirus vaccine derived from the most common circulating wild-type rotavirus strain G1P[8]. Rotarix is based on a rotavirus of human origin and is administered to infants in two oral doses with an interval of at least four weeks between doses. The manufacturer states that the "vaccination course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks" (EMA 2011). As of May 2016, Rotarix had been introduced in national immunization programmes in 63 countries around the world (PATH 2016).

RotaTeq is an oral, live, human-bovine, reassortant, multivalent rotavirus vaccine developed from an original Wistar calf 3 (WC3) strain of bovine rotavirus. The vaccine contains five live, human-bovine reassortant rotavirus strains. Four reassortant rotavirus strains each express one of the common human VP7 (G) types including G1, G2, G3, and G4, and the fifth reassortant expresses the common human VP4 (P) type P[8]. The three-dose liquid vaccine is intended for infants aged between six and 32 weeks, with the first dose given at six to 12 weeks and subsequent doses administered at four- to 10-week intervals; however, the third dose should not be given after 32 weeks of age (Merck 2008). As of May 2016, RotaTeq had been introduced in national immunization programmes in 22 countries around the world (PATH 2016).

Rotavac is an oral live-attenuated, monovalent vaccine derived from a naturally-occurring reassortant G9P[11] strain [116E] isolated from a newborn child in India (Yen 2014). This oral vaccine was developed by Bharat Biotech Ltd. in India and was licensed in India in 2014 (VAC Chandola 2017-IND). Three doses are recommended, to be administered at 6, 10, and 14 weeks of age.

Rotasiil is an oral, live, human-bovine, reassortant, multivalent rotavirus vaccine. The vaccine contains five live, human-bovine reassortant rotavirus strains (G1, G2, G3, G4, and G9). This vaccine was developed by the Serum Institute of India Ltd. and nationally licensed in 2017. Three doses are recommended, to be administered at 6, 10, and 14 weeks of age, at the same time as routine vaccinations under India's childhood immunization schedule.

There are a further two rotavirus vaccines that have been licensed and approved for use in individual countries, but are not yet prequalified by the WHO: Lanzhou lamb rotavirus vaccine (LLR; Lanzhou Institute of Biomedical Products) which is licensed and used in China; and a monovalent vaccine (Rotavin-M1, POLYVAC) which is licensed and used in Vietnam.

Vaccines no longer in use

Several vaccines, including the first licensed rotavirus vaccine (RRV-TV; RotaShield, Wyeth Laboratories), were developed, tested in trials, and later abandoned or withdrawn from use. These vaccines are included in a separate Cochrane Review (Soares-Weiser 2004). RRV-TV, a tetravalent rhesus-human reassortant vaccine, was withdrawn from use in 1999 following reports of intussusception (bowel obstruction which occurs when one segment of bowel becomes enfolded within another segment). Evaluations have since suggested that the risk of developing intussusception was age-related, with 80% of intussusception cases occurring in infants who were more than 90 days old when the first vaccine dose was administered (Simonsen 2005). Although it is still currently licensed, this vaccine is no longer in clinical use (Dennehy 2008).

How the intervention might work

Recommendations for rotavirus vaccine use

Vaccination with Rotarix and RotaTeq was first recommended in 2006 in Europe and the Americas, where clinical trials had demonstrated vaccine efficacy of 85% to 100% (RIX Ruiz-Palac 06-LA/EU; TEQ Vesikari 2006b-INT). In April 2009, following clinical trials of Rotarix and RotaTeq in low- and middle-income countries in Africa and Asia, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization recommended "the inclusion of rotavirus vaccination of infants into all national immunization programmes", with a stronger recommendation for countries where "diarrhoeal deaths account for ≥ 10% of mortality among children aged < 5 years" (SAGE 2009). Due to an age-related risk of intussusception identified with RRV-TV (Murphy 2001), SAGE recommended administering the first dose of Rotarix or RotaTeq to infants of six to 15 weeks of age, with the last dose administered before 32 weeks of age (SAGE 2009). In April 2012, SAGE relaxed the age-restricted recommendation and advised to vaccinate "as soon as possible after the age of six weeks" because "the current age restrictions for the first dose (< 15 weeks) and last dose (< 32 weeks) are preventing vaccination of many vulnerable children" (Patel 2012; SAGE 2012). Rotavac and Rotasiil, which have been prequalified for use by the WHO, are nationally licensed in India and were recommended for use by SAGE in 2020 (WHO 2020).

Performance of oral rotavirus vaccines by setting

Many orally administered vaccines, including rotavirus vaccines, have demonstrated lower immunogenicity and efficacy in low- and middle-income countries in Africa and Asia compared to high-income countries in North America, South America, and Europe (Levine 2010). A systematic review demonstrated a correlation between lower vaccine efficacy against severe rotavirus diarrhoea, and high child mortality rates (Fischer Walker 2011). The reasons for reduced oral vaccine efficacy in countries with higher child mortality rates are unknown; factors may include interference by maternal antibody, environmental enteropathy, co-administration with oral poliovirus vaccine, histoblood group antigen, diverse rotavirus strain types, micronutrient deficiencies, and altered gut microbiota (Czerkinsky 2015; Parker 2018).

Outcomes of interest

The safety and efficacy of the licensed vaccines for the prevention of rotavirus gastroenteritis in infants have been assessed in several randomized controlled trials (RCTs) worldwide. The goal of this review is to systematically assess these trials and to evaluate vaccine efficacy against severe rotavirus diarrhoea and severe all-cause diarrhoea, within the first year of life and up to two years of age. We also examine the occurrence of deaths and serious adverse events, including intussusception, to provide decision makers, clinicians, and caregivers with the relevant information to aid decisions about vaccine use.

Why it is important to do this review

Development of Cochrane systematic rotavirus vaccine reviews

The original Cochrane Review of rotavirus vaccines (Soares-Weiser 2004) examined vaccines in use and other vaccines, including those that were no longer in use or were in development. Soares-Weiser 2004 concluded that more trials were needed before routine vaccine use could be recommended. An update in 2009 included a new search, revised inclusion criteria (only vaccines in use in children), and updated review methods and new authors. The review was updated again in 2010 with nine new studies (Soares-Weiser 2010). The 2010 version of the review concluded that Rotarix and RotaTeq are both effective vaccines for the prevention of rotavirus diarrhoea. Another update in February 2012 added a further nine new studies, GRADE 'Summary of findings' tables and, again, new authors joined the team (Soares-Weiser 2012a). The November 2012 update included a new search, and major restructuring of analyses, including re-evaluating primary outcomes in consultation with the WHO to reflect the observation that vaccine efficacy profiles are different in countries with different mortality rates (Soares-Weiser 2012b). The previous update published in 2019 (Soares-Weiser 2019) added a further 10 Rotarix and RotaTeq studies to the review and, for the first time, four studies of Rotavac. This update added another five studies of a new vaccine Rotasiil, that has been prequalified by the WHO since the previous version of the review (Table 1).

OBJECTIVES

To evaluate rotavirus vaccines prequalified by the WHO (Rotarix, RotaTeq, Rotasiil, and Rotavac) for their efficacy and safety in children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Children (age as defined in the trials).

Types of interventions

Intervention

Rotavirus vaccines approved by the WHO vaccine prequalification programme (Dellepiane 2015; WHO 2021a).

Control

Placebo, no vaccination, or other vaccine.

Types of outcome measures

Primary outcomes

We selected our primary outcome measures in consultation with the WHO, and stratified them according to low-, medium-, or high-mortality rate, based on country under-five mortality rates taken from the UNICEF report on levels and trends in child mortality (UNICEF 2019). Efficacy outcomes were collected for up to one year and up to two years follow-up. In addition, the severe rotavirus diarrhoea outcome was collected for the second year of life.

- Rotavirus diarrhoea: severe (as defined in trial report)
- All-cause diarrhoea: severe
- All-cause death
- Serious adverse events (that are fatal, life-threatening, or result in hospitalization)
- Intussusception

Secondary outcomes

- Rotavirus diarrhoea: of any severity
- All-cause diarrhoea (as defined in trial report)
- Rotavirus diarrhoea: requiring hospitalization
- All-cause diarrhoea: requiring hospitalization
- Emergency department visit
- Hospital admission: all-cause
- Reactogenicity (capacity to produce an adverse reaction, such as fever, diarrhoea, and vomiting)
- Adverse events that require discontinuation of vaccination schedule
- Dropouts

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and ongoing).

Electronic searches

For this review update, Dr Vittoria Lutje (Information Specialist, Cochrane Infectious Diseases Group) searched the following databases using the search terms and strategy described in Appendix 10.

- Cochrane Infectious Diseases Group Specialized Register (30 November 2020)
- Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (2020, Issue 11)
- MEDLINE (via PubMed; 1966 to 30 November 2020)
- Embase (1974 to 30 November 2020)
- LILACS (1982 to 30 November 2020)
- Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index-Science (CPCI-S), Conference Proceedings Citation Index-Social Science & Humanities (CPCI-SSH), all via Web of Science, 1990-30 November 2020.

Searching other resources

We also searched the WHO International Clinical Trials Registry Platform (ICTRP) and the Clinicaltrials.gov Clinical Study Register (www.clinicaltrials.gov).

We searched manufacturers' websites for clinical trial reports. We also checked the reference lists of relevant systematic reviews and included studies.

Data collection and analysis

Selection of studies

For this review update, we uploaded and screened references in DistillerSR online. Two review authors independently screened each title and abstract identified in the search. We retrieved full texts for potentially relevant references and two review authors again screened them independently, resolving disagreements by recourse to a third review author. We tabulated the excluded studies along with the reason for excluding them in the Characteristics of excluded studies tables. We ensured that data from each trial were entered only once in our review. In previous versions of this review, we had screened references in an EndNote database.

Data extraction and management

We created Microsoft Excel forms for data collection, which were piloted and then revised after the review author team's discussion. For previous versions of this review, we had used Microsoft Word or Excel data collection forms.

One review author extracted data and another review author cross-checked them. All outcomes were dichotomous, and we extracted the total number of participants and the number of participants who experienced the event. We cross-checked the extracted data to identify errors, resolving disagreements by referring to the trial report or by consulting a third review author. One review author entered data into Review Manager 5 for previous versions of this review (RevMan 2014), or RevMan Web for this review update version (RevMan Web 2021).

The use and mentioning of trade names in this review represents no endorsement of or advertisement for any product. The use of trade names was unavoidable as no generic names were identified for some of the vaccines evaluated here.

Assessment of risk of bias in included studies

Two review authors independently assessed the risks of bias of each trial, using the Cochrane Risk of bias tool (Higgins 2017). Based on the guidance of the Cochrane Risk of bias tool (Higgins 2017), we created a form to make judgements on the risk of bias for the rotavirus diarrhoea outcome measure in six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other potential sources of bias. We categorized these judgements as ‘low', ‘high', or ‘unclear' risk

of bias. We resolved disagreements through discussion with a third review author.

For the 2012 published version of this review, we asked for help from Dr Ana Maria Restrepo at the WHO Initiative for Vaccine Research, who contacted the vaccine manufacturers GlaxoSmithKline (Rotarix) and Merck (RotaTeq), who were involved in designing and funding most of the included trials. We provided them with an Excel spreadsheet with specific details of each trial that would impact on the assessment of risk of bias. We received details from Merck (RotaTeq) (see Characteristics of included studies for details). For the 2019 review update, we matched most of the previously-included Rotarix studies to the full clinical trial reports available on the manufacturer's website (www.gsk-clinicalstudyregister.com). More details were available in these trial reports than in the published studies, that were helpful in assessing the risks of bias for these studies.

Measures of treatment effect

We analysed dichotomous data of cases by calculating the risk ratio (RR) for each trial (expressed using blue squares in forest plots) with the uncertainty in each result expressed using 95% confidence intervals (CIs). For dichotomous data of events that could occur more than once in one participant, we calculated the rate ratio (expressed using red squares in forest plots) on the logarithmic scale using the generic inverse variance method (see Data synthesis for more details). For outcomes that included cluster-RCTs we calculated risk ratios (expressed using red squares in forest plots) using the generic inverse variance method (see Unit of analysis issues for more details).

Unit of analysis issues

When trials had multiple treatment arms and we considered it suitable, we grouped the trial arms. We excluded irrelevant trial arms.

We pooled cluster-RCT data that had been adjusted for clustering with data from trials that randomly assigned individuals (individual-RCTs). For outcomes that included cluster-RCTs, we pooled risk ratios on the logarithmic scale with their standard errors using the generic inverse variance method (16.3.3. in Higgins 2011). When the results of a cluster-RCT had not been adjusted for clustering, we imputed the clustering effect (intra-cluster correlation coefficient (ICC)) from another study, and performed sensitivity analyses excluding these studies.

Dealing with missing data

We undertook a complete-case analysis (the number analysed) and an intention-to-treat analysis when data were available.

Assessment of heterogeneity

We initially assessed heterogeneity in the results of the trials by inspecting the graphical presentations and by calculating the Chi^2 test of heterogeneity. However, we were aware of the fact that the Chi^2 test has a poor ability to detect statistically significant heterogeneity among studies. We therefore also quantified the impact of heterogeneity in the meta-analysis using a measure of the degree of inconsistency in the studies' results (Higgins 2003). This measure (the I^2 statistic) describes the percentage of total variation across studies that are due to heterogeneity rather than to the play of chance (Higgins 2003). The I^2 statistic values lie between 0% and 100%, and a simplified categorization of heterogeneity could be low, moderate, and high for I^2 statistic values of 25%, 50%, and 75% respectively (Higgins 2003).

Assessment of reporting biases

If 10 or more studies were included in an outcome, we examined a funnel plot for the primary outcome (severe rotavirus diarrhoea), estimating the precision of trials (plotting the RR against the standard error (SE) of the log of RR) to estimate potential asymmetry.

Data synthesis

We stratified all analyses by the type of vaccine, Rotarix, RotaTeq, Rotasiil, or Rotavac. Subsequently, we grouped all outcomes in the meta-analyses according to the time point when the outcome was measured or the number of rotavirus seasons, or both, as follows: less than two months; up to one year (one rotavirus season); up to two years (up to two rotavirus seasons); and up to three years (three rotavirus seasons). For severe rotavirus diarrhoea, we also reported on cases during the second year of life (or during the second rotavirus season). If data were available for more than one time point, we used the number of completely vaccinated children for each time point in the trial.

For the current update, we stratified each primary outcome (rotavirus diarrhoea, all-cause diarrhoea, all-cause death, all serious adverse events, and intussusception) and selected secondary efficacy outcomes (rotavirus diarrhoea and all-cause diarrhoea of any severity, and all-cause hospitalization) by country under-five mortality rates taken from the UNICEF report on levels and trends in child mortality (UNICEF 2019), as follows:

- Low-mortality countries: those in the lowest quartile of under-five child mortality rates
- Medium-mortality countries: those in the second quartile of under-five child mortality rates
- High-mortality countries: those in the highest two quartiles of under-five child mortality rates

We used a random-effects model for all meta-analyses.

We included separate analyses for cases of diarrhoea (e.g. a child who has diarrhoea regardless of the number of episodes) and episodes (i.e. one child can experience more than one episode), where data permitted. We combined episodes using the rate ratio in the logarithmic scale and SE, with the uncertainty in each result being expressed using a 95% CI (9.4.8. in Higgins 2011).

Subgroup analysis and investigation of heterogeneity

In addition to stratifying the results by country-based low-, medium-, or high-mortality, we planned to perform subgroup analyses to assess the impact of the following possible sources of heterogeneity for any of the included vaccines: vaccine protection against specific rotavirus serotypes; and vaccination of special groups, including immunocompromised (such as HIV-infected) children and children with malnutrition. In previous versions of this review (Soares-Weiser 2010; Soares-Weiser 2012a), we also analysed vaccine effect according to each study's country income, use of other childhood vaccines, number of doses administered, source of funding, and whether infants were born prematurely or were breast- or formula-fed. These subgroup analyses did not show

any differences, and were not presented in subsequent updates of this review; they can be found in Soares-Weiser 2010 and Soares-Weiser 2012a.

To get a more stable estimate for intussusception, which is a very rare event, we also included a post hoc subgroup analysis where we analysed the risk of intussusception with any vaccine compared with placebo by country mortality setting and overall (Table 2).

Sensitivity analysis

We conducted sensitivity analyses excluding cluster-randomized studies.

We also planned to conduct sensitivity analyses for the primary outcomes according to allocation concealment (high, low, and unclear risk of bias) for outcomes in which data could not be pooled because of significant heterogeneity (I^2 statistic > 75%).

Summary of findings and assessment of the certainty of the evidence

We interpreted the findings of this review using the GRADE approach (Schünemann 2017), and we used GRADE profiler (GRADE 2004) to import data from RevMan 5 (RevMan 2014) to create summary of findings tables. These tables provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient care and decision making, and is reflected as follows: high certainty ("vaccine prevents...."); moderate certainty ("vaccine probably prevents..."); low certainty ("vaccine may prevent...."); and very low certainty ("we do not know whether or not the vaccine prevents....").

We selected primary outcomes, all stratified by vaccine and high or low country mortality, for inclusion in the summary of findings tables: severe rotavirus diarrhoea at up to one year and up to two years follow-up; severe all-cause diarrhoea at up to one year and up to two years follow-up; all-cause death; serious adverse events; and intussusception.

RESULTS

Description of studies

Results of the search

The update search in November 2020 identified 300 records after de-duplication and an additional five studies that were retrieved from the excluded studies list. We screened 305 records and considered 282 to be irrelevant. We reviewed the full text of 23 studies. We excluded 18 studies for this update. Together with the previously 31 excluded studies, there are now 49 excluded studies in this review. The current update of the review includes 60 independent trials (see Characteristics of included studies), five of which are new to this update (SIIL Isanaka 2017-NER; SIIL Kulkarni 2017-IND; SIIL Zade 2014-INDa; SIIL Zade 2014-INDb; SIIL Zade 2014-INDc).

Included studies

The 60 included trials enrolled about 228,233 participants (approximate number, as some trials provided only the number evaluable), and each trial compared a rotavirus vaccine with a placebo or no intervention. The vaccines tested were Rotarix (36 trials reported in 171 publications or reports; 119,114 participants), RotaTeq (15 trials reported in 60 publications or reports; 88,934 participants), Rotasiil (five trials reported in 11 publications or reports; 11,753 participants), and Rotavac (four trials reported in 13 publications or reports; 8432 participants).

The trials were conducted in Africa, Asia, Europe, and the Americas, and the location can be identified in the study reference: AF, Africa; AS, Asia; EU, Europe; INT, several international locations; LA, Latin America; NA, North America; or country three-letter acronym according to ISO 3166-1 Alpha-3 (e.g. BGD for Bangladesh) from www.all-acronyms.com/special/countries_acronyms_and_abbreviations, if the study was conducted in a single country.

1. Rotarix

The 36 Rotarix trials were published between 1998 and 2017. Five of the trials are unpublished and were located on the GlaxoSmithKline website through clinicalstudyresults.org or clinicaltrials.gov. One trial (RIX Madhi 2010-AF) provided country-specific data for efficacy outcomes but not for safety outcomes, and was consequently split into RIX Madhi 2010-MWI and RIX Madhi 2010-ZAF for the Malawi- and South Africa-specific data. Twenty-five trials enrolled around 500 participants or fewer, three trials enrolled around 1000 participants, seven trials enrolled between 2155 and 12,318 participants, and one large trial enrolled 63,225 participants. Most children were aged between one and three months at the time of the first vaccination.

Population

Most trials included healthy infants. Two trials included HIV-infected or -exposed infants (RIX Madhi 2010-AF; RIX Steele 2010a-ZAF), one trial included premature infants (RIX Omenaca 2012-EU), and one trial included children aged two to six years (RIX Li 2013a-CHN).

Outcome measures

Each trial reported on one or more of the outcome measures specified for this review (see Appendix 1). We included data on participants requiring medical visits, as this was reported in some trials and is a similar outcome measure to participants requiring hospitalization.

Twenty-three trials were safety studies, reporting mainly safety outcomes (e.g. serious adverse events and reactogenicity). Eleven of these trials also reported efficacy outcomes (e.g. rotavirus diarrhoea) with a follow-up of up to two months. Two trials reported on efficacy or effectiveness but not safety (RIX Colgate 2016-BGD; RIX Zaman 2017-BGD). The trials varied in the length of follow-up, but in general the trials that specified efficacy outcome measures had longer follow-up times (Appendix 1).

As shown in Appendix 2, rotavirus diarrhoea (of any severity) was the most common efficacy outcome reported (by 23 trials); 14 trials reported on severe rotavirus diarrhoea, and 10 reported on rotavirus diarrhoea requiring hospitalization. Data on all-cause diarrhoea were provided by 17 trials, and severe all-cause diarrhoea by nine trials. Most reported all-cause death and dropouts, but other efficacy outcomes were reported by few trials.

For safety outcomes (Appendix 3), 29 trials reported on reactogenicity, all but four trials reported on serious adverse events, and 24 reported on adverse events leading to discontinuation of the intervention.

Location

Early trials were conducted in North America and Europe, but since 2005 trials have also been conducted in Asia (Bangladesh, China, India, Japan, Philippines, South Korea, Singapore, Thailand, Vietnam; 17 trials), Latin America (Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, Venezuela; six trials), and Africa (South Africa, Malawi; four trials); see Appendix 4. Most trials had multiple sites, often in several countries; RIX Vesikari 2007a-EU included 98 sites in six European countries.

Country mortality rate

Fourteen trials were conducted in countries with low-mortality rates, ten trials in medium-mortality countries, and 12 trials were conducted in countries with high-mortality rates; see Appendix 4. For RIX Madhi 2010-AF, available data were split between countries into RIX Madhi 2010-MWI and RIX Madhi 2010-ZAF. Three trials were conducted in several countries with both low and medium, or medium and high mortality: RIX Ruiz-Palac 06-LA/EU was conducted mainly in medium-mortality countries in Latin America (Argentina, Brazil, Chile, Colombia, Mexico, Panama, Peru), but also in low-mortality Finland, and in four high-mortality countries (Dominican Republic, Honduras, Nicaragua, Venezuela), and was placed in the medium-mortality group. RIX Salinas 2005-LA was mainly conducted in medium-mortality Brazil and Mexico but also in high-mortality Venezuela and was placed in the medium-mortality group. Finally, RIX Tregnaghi 2011-LA was also mainly conducted in medium-mortality countries (Argentina, Brazil, Colombia, Panama) but also in high-mortality Dominican Republic and Honduras and was placed in the medium-mortality group.

Vaccine schedule

The trials varied in the vaccine dose and schedule (see Appendix 5). Most trials gave two doses of the vaccine with virus concentration of more than 10^6 plaque-forming units (PFUs). Older trials, conducted between 1998 and 2005, tended to include slightly lower PFUs or a range of PFUs for comparison.

Rotarix was given as two doses in all but five trials: one trial conducted in partnership with GlaxoSmithKline and PATH Rotavirus Vaccine Program tested two and three doses of the vaccine (RIX Madhi 2010-AF); another trial conducted by GlaxoSmithKline in which the poliovirus vaccine was co-administered with Rotarix, tested two or three vaccine doses to investigate differences in immune response (RIX Steele 2010b-ZAF); a third study tested three vaccine doses in HIV-positive infants (RIX Steele 2010a-ZAF); a fourth study tested three vaccine doses in healthy infants (RIX GSK[021] 2007-PAN); a fifth study, that included children aged two to six years, administered one dose only (RIX Li 2013a-CHN).

Some trials compared more than one intervention arm: different PFU virus concentrations (RIX Vesikari 2004a-FIN; RIX Dennehy 2005-NA; RIX Phua 2005-SGP; RIX Salinas 2005-LA; RIX Ward 2006-USA); different formulations (RIX GSK[021] 2007-PAN; RIX GSK[033] 2007-LA; RIX GSK[101555] 2008-PHL; RIX Kerdpanich 2010-THA; RIX Vesikari 2011-FIN); co-administration of other vaccine (RIX Steele 2008-ZAF; RIX Zaman 2009-BGD; RIX NCT00158756-RUS; RIX Li 2014-CHN); and different intervals between doses (RIX Anh 2011-PHL; RIX Anh 2011-VNM).

Infant vaccination status

All but four trial reports referred to vaccination with other infant vaccines (see Appendix 5). Most trials co-administered other routine infant vaccines, such as diphtheria-tetanus-acellular pertussis (DTaP), *Haemophilus influenzae* type b (HiB), inactivated polio vaccine (IPV), and hepatitis B vaccine (HBV). Some trials also co-administered oral polio vaccine (OPV). Other trials imposed a two-week separation between other infant vaccines and rotavirus vaccine or placebo, or specified other vaccines as not allowed.

Methods for collecting adverse event data

Fifteen of the 36 trials did not provide details of how adverse event data were collected. Out of the trials that did report the method of collecting adverse event data, 13 trials used passive methods (e.g. diary cards), two used an active method ("active surveillance system"), and five used both passive and active methods (e.g. diary card plus regular telephone calls to parents); see Appendix 6.

Source of funding

Most trials were supported by GlaxoSmithKline Biologicals, three of which were in partnership with PATH Rotavirus Vaccine Program (RIX Li 2014-CHN; RIX Madhi 2010-AF; RIX Zaman 2009-BGD), and another two in partnership with RAPID trials and the WHO (RIX Steele 2008-ZAF; RIX Steele 2010a-ZAF). One trial was funded by The Bill and Melinda Gates Foundation (RIX Colgate 2016-BGD) and one by GAVI and PATH (RIX Zaman 2017-BGD). Three trials were sponsored by Avant Immunotherapeutics (formerly Virus Research Institute, Inc.) (RIX Bernstein 1998-USA; RIX Bernstein 1999-USA; RIX Ward 2006-USA).

2. RotaTeq

We identified 15 trials of RotaTeq vaccine. The earliest was reported in 2003 and the most recent in 2017. One of the trials is unpublished and was accessed via clinicalstudyresults.org. Two trials (TEQ Armah 2010-AF and TEQ Zaman 2010-AS) provided country-specific data for some outcomes but not for all outcomes, and were consequently split into TEQ Armah 2010-GHA; TEQ Armah 2010-KEN; and TEQ Armah 2010-MLI for the Ghana-, Kenya-, and Mali-specific data, and TEQ Zaman 2010-BGD and TEQ Zaman 2010-VNM for the Bangladesh- and Vietnam-specific data. Overall, 88,934 participants were included in the trials; the largest trial included 70,301 participants (TEQ Vesikari 2006b-INT) and the smallest included 48 participants (TEQ Lawrence 2012-CHN). For the 2012 update of this review, we received new information from Merck (Merck 2012) for some of the trials on the outcomes, serious adverse events, intussusception, and deaths. We have incorporated the new information into the analyses and have indicated this in the Characteristics of included studies section.

Population

Most trials included healthy infants. One trial included both healthy and HIV-infected infants (TEQ Armah 2010-KEN), another trial included HIV-exposed but uninfected and HIV-infected infants (TEQ Levin 2017-AF), and one trial included prematurely-born infants as well as those born at normal gestation (TEQ Vesikari 2006b-INT). All

but two trials enrolled children aged between one month and three months; the children in TEQ Vesikari 2006a-FIN were aged between three months and six months, and there was a child cohort (2- to 6-year-old children) in addition to an infant cohort in TEQ Lawrence 2012-CHN.

Outcome measures

Six trials were safety studies (Appendix 1), reporting safety outcomes (e.g. serious adverse events and reactogenicity). The other nine trials reported one or more efficacy and safety outcomes (Appendix 1). The trials varied in the length of follow-up (Appendix 1), but in general the trials that specified efficacy outcome measures had longer follow-up times (up to three years). Similar to the Rotarix trials, we included data on participants requiring medical visits, as this was reported in some trials and is a similar outcome measure to participants requiring hospitalization.

As shown in Appendix 2, rotavirus diarrhoea, severe cases and cases of any severity, were the most common efficacy outcomes reported (by eight trials); only one of these reported rotavirus diarrhoea requiring hospitalization. Three trials provided data on severe cases of all-cause diarrhoea; two also presented data on cases with any severity. Eleven trials reported all-cause death, and 13 of the 15 trials reported dropouts.

For safety outcomes, all trials reported on serious adverse events and reactogenicity, and 13 trials reported on adverse events leading to discontinuation of the intervention; see Appendix 3.

Location

Half of the trials were conducted in low-mortality countries in North America and Europe. Six trials, including the smallest and the largest trials, were conducted in other regions: TEQ Armah 2010-AF was conducted in Ghana, Kenya and Mali; TEQ Levin 2017-AF was conducted in Botswana, Tanzania, Zambia and Zimbabwe, TEQ Dhingra 2014-IND was conducted in India, TEQ Kim 2008-KOR was conducted in South Korea; TEQ Iwata 2013-JPN was conducted in Japan; TEQ Lawrence 2012-CHN and TEQ Mo 2017-CHN were conducted in China; TEQ Vesikari 2006b-INT was conducted in 12 countries in Asia, the Caribbean, Europe, Latin America, North America; and TEQ Zaman 2010-AS was conducted in Bangladesh and Vietnam. Each trial had multiple sites, ranging from three (TEQ Vesikari 2006a-FIN) to 356 sites (TEQ Vesikari 2006b-INT); see Appendix 4.

Country mortality rate

Nine trials were conducted in countries with low-mortality rates, two trials were conducted in medium-mortality countries, and four trials in high-mortality countries; see Appendix 4. TEQ Armah 2010-AF was conducted in three high-mortality countries, Ghana, Kenya, and Mali and, when available, the data were split into TEQ Armah 2010-GHA, TEQ Armah 2010-KEN and TEQ Armah 2010-MLI. TEQ Zaman 2010-AS was conducted in high-mortality Bangladesh and Vietnam and, when available, the data were split into TEQ Zaman 2010-BGD and TEQ Zaman 2010-VNM. TEQ Vesikari 2006b-INT was conducted mainly in European and American low-mortality countries (Belgium, Finland, Germany, Italy, Puerto Rico, Sweden, Taiwan, USA), but also in medium-mortality countries (Costa Rica, Jamaica, Mexico) and high-mortality Guatemala, and was placed in the low-mortality group.

Vaccine schedule

Each trial used three doses of RotaTeq vaccine, with intervals between doses of four and 10 weeks (see Appendix 5). All but two trials had one vaccine and one placebo arm; TEQ Vesikari 2006a-FIN included three vaccine arms in which there were different RotaTeq components (G1-4, P1A, G1-4, and P1A), and TEQ Dhingra 2014-IND included a RotaTeq arm, a placebo arm, and three arms with different concentrations of BRV-TV vaccine.

Infant vaccination status

Most trials did not restrict the use of other childhood vaccines (see Appendix 5). Two trials co-administered HBV, diphtheria-tetanus-pertussis (DTP), poliovirus, and Hib vaccines with RotaTeq (TEQ Ciarlet 2009-EU; TEQ Dhingra 2014-IND). One trial randomized participants to either concomitant or staggered administration of other childhood vaccines (OPV, DTaP) with RotaTeq or placebo (TEQ Mo 2017-CHN). Three trials allowed the use of OPV, in addition to other licensed childhood vaccines (TEQ Armah 2010-AF; TEQ Mo 2017-CHN; TEQ Zaman 2010-AS). Three trials did not allow the use of other vaccines (TEQ Clark 2003-USA; TEQ Clark 2004-USA; TEQ Lawrence 2012-CHN), and one trial did not mention their use (TEQ Iwata 2013-JPN).

Methods for collecting adverse event data

As shown in Appendix 6, seven trials used a combination of passive methods (e.g. diary cards for parents) and active methods (directly contacting parents) to collect adverse event data. The other trials used passive methods only (diary cards, three trials), active methods only ("active surveillance", three trials), or the information was not provided (two trials).

Source of funding

All but one trial was funded by Merck & Co., Inc. Two of those trials also received funding and were run by PATH (GAVI Alliance grant) (TEQ Armah 2010-AF; TEQ Zaman 2010-AS), and one trial also received funding from the International Maternal, Pediatric, and Adolescent AIDS Clinical Trial Network (IMPAACT) through the National Institute of Health (TEQ Levin 2017-AF). One trial was funded by Shantha Biotechnics Ltd (TEQ Dhingra 2014-IND).

3. Rotasiil

We identified five trials of Rotasiil vaccine. The earliest was reported in 2014 and the most recent in 2017. Overall, 11,753 participants were included in the trials; the largest trial included 7505 participants (SIIL Kulkarni 2017-IND) and the smallest included 36 participants (SIIL Zade 2014-INDa).

Population

All trials included healthy infants. Trials enrolled infants aged between six weeks and ten weeks. SIIL Zade 2014-INDa also enrolled 18 toddlers (age not specified) and 18 adults (not included in the review).

Outcome measures

Three trials were safety studies (Appendix 1) reporting safety outcomes and immunogenicity outcomes. They reported on follow-up results for up to one month after the last vaccine dose. The other two trials (SIIL Isanaka 2017-NER; SIIL Kulkarni 2017-IND) reported on efficacy, safety, and immunogenicity outcomes until the infants were two years of age.

For safety outcomes, all trials reported on serious adverse events and four reported on reactogenicity.

Location

Four trials were conducted in India, three of them in Pune and one trial in six sites in Pune, Kolkata, Sewagram, Delhi, Manipal, and Jammu (SIIL Kulkarni 2017-IND). One trial (SIIL Isanaka 2017-NER) was conducted in Niger (one site in Madarounfa).

Country mortality rate

All trials were conducted in countries with high-mortality rates (India and Niger).

Vaccine schedule

Four trials used three doses of Rotasiil vaccine with an interval of four weeks between the doses. One trial (SIIL Zade 2014-INDa) administered one dose. All five trials had one vaccine and one placebo arm.

Infant vaccination status

Two trials co-administered other routine childhood vaccines (OPV, DTP, HBV and Hib) with Rotasiil (SIIL Isanaka 2017-NER; SIIL Kulkarni 2017-IND). One trial separated the use of other routine childhood vaccines from Rotasiil administration by at least one week (SIIL Zade 2014-INDc). Two studies did not report on vaccination with other childhood vaccines (SIIL Zade 2014-INDa; SIIL Zade 2014-INDb).

Methods for collecting adverse event data

Two trials used a combination of passive methods (e.g. diary cards for parents) and active methods (home visits) to collect adverse event data (SIIL Isanaka 2017-NER; SIIL Kulkarni 2017-IND). The remaining three trials did not provide information on methods for collecting adverse event data.

Source of funding

The four trials conducted in India were funded by the Serum Institute of India, and one of them was also co-funded by PATH (SIIL Kulkarni 2017-IND). The study conducted in Niger (SIIL Isanaka 2017-NER) was funded by Médecins sans Frontières and the Kavli Foundation, and the Serum Institute of India donated vaccine and placebo.

4. Rotavac

We identified four trials of Rotavac vaccine. The earliest was reported in 2006 and the most recent in 2017. Overall, 8432 participants were included in the trials; the largest trial included 6799 participants (VAC Bhandari 2014-IND) and the smallest included 90 participants (VAC Bhandari 2006-IND).

Population

All trials included healthy infants. Trials enrolled infants aged between six weeks and nine weeks.

Outcome measures

Three trials were safety studies (Appendix 1) reporting safety outcomes. They reported on follow-up results for one to 12 months after the last vaccine dose. The other trial (VAC Bhandari 2014-IND) reported on efficacy, safety, and immunogenicity outcomes until the infants were two years of age.

As shown in Appendix 2, VAC Bhandari 2014-IND reported on rotavirus diarrhoea (severe cases, cases of any severity, and cases requiring medical attention). The same trial also provided data on severe cases of all-cause diarrhoea. Two trials reported all-cause death, and three of the four trials reported dropouts.

For safety outcomes, all trials reported on serious adverse events and two reported on reactogenicity.

Location

All trials were conducted in India, one at three sites in the cities of Delhi, Pune, and Vellore (VAC Bhandari 2014-IND), and the remaining three studies at one site in Delhi.

Country mortality rate

All trials were conducted in India, a country with a high-mortality rate.

Vaccine schedule

Most trials used three doses of Rotavac vaccine, with intervals between doses of four to eight weeks (see Appendix 5). One trial (VAC Bhandari 2006-IND) administered one dose. One trial had one vaccine and one placebo arm (VAC Bhandari 2014-IND). VAC Bhandari 2006-IND included an additional vaccine arm for a rotavirus vaccine candidate (I321) that we did not include for analysis in this review. VAC Bhandari 2009-IND randomized participants to high- (1×10^5 ffu) and low-dose (1×10^4 ffu) vaccine arms which we combined in this review. VAC Chandola 2017-IND randomized participants to three vaccine production lots as well as to placebo. We combined the different production lot arms in our analyses.

Infant vaccination status

Two trials separated the use of other routine childhood vaccines from Rotavac administration by at least two weeks (VAC Bhandari 2006-IND; VAC Bhandari 2009-IND). Two trials co-administered other routine childhood vaccines (OPV, DTP, HBV and Hib) with Rotavac (VAC Bhandari 2014-IND; VAC Chandola 2017-IND).

Methods for collecting adverse event data

As shown in Appendix 6, three trials used a combination of passive methods (e.g. diary cards for parents) and active methods (directly contacting parents) to collect adverse event data. The other trial (VAC Chandola 2017-IND) used active methods only (directly contacting parents).

Source of funding

One trial was funded by Bharat Biotech (VAC Bhandari 2006-IND), one trial was co-funded by Bharat Biotech (VAC Bhandari 2009-IND) and the other two trials were funded by PATH, the Government of India, and other not-for-profit organisations (VAC Bhandari 2014-IND; VAC Chandola 2017-IND).

5. Studies awaiting classification

There are no studies awaiting classification.

6. Ongoing studies

We did not identify any relevant ongoing trials.

Excluded studies

There are 49 excluded studies (Figure 2). Eighteen of these excluded studies are new to this update. We excluded 31 studies because they reported on comparisons not relevant to this review, nine because they reported on irrelevant outcomes, six because they reported on unlicensed vaccines in development, two because they reported on licensed vaccines that have not been prequalified by the WHO, and one because it reported on a withdrawn rotavirus vaccine.

Figure 2.

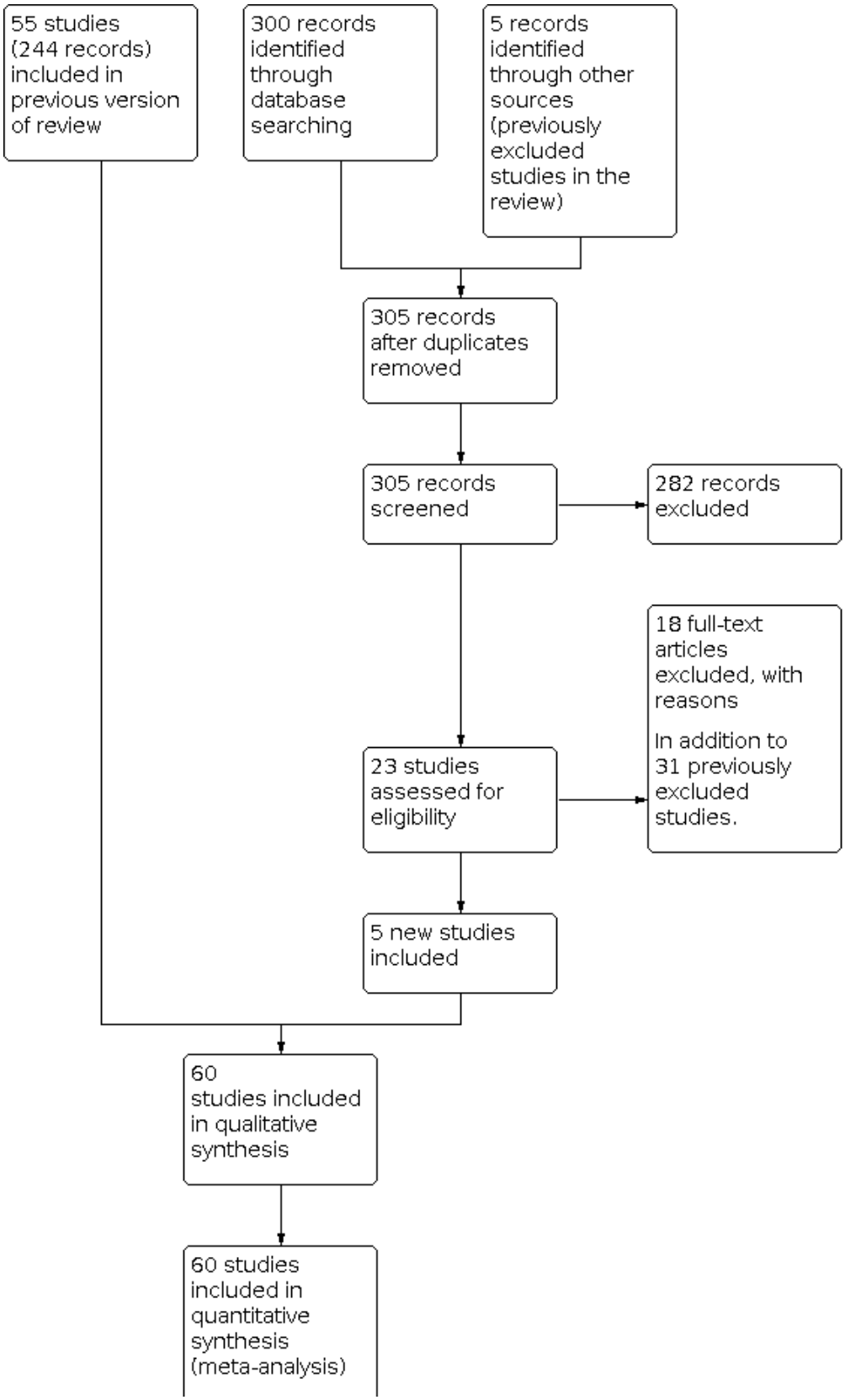


Figure 2. (Continued)

(meta-analysis)

We moved five excluded studies from the list in the previously published version of this review to the included studies list because they now qualify for inclusion.

We removed 42 excluded studies from the list in the previously published version of this review because the list had become very long and these studies clearly did not qualify for inclusion: 22 were observational studies, 11 were trial registration records without outcome results of irrelevant trials, six were not primary research studies, and three did not assess a rotavirus vaccine. These references can be found in the previously published version of this review (Soares-Weiser 2019).

Risk of bias in included studies

Risk of bias was assessed for each trial, with a focus on the rotavirus diarrhoea outcome measure. Overall pictorial summaries of the risk of bias assessments are shown in Figure 3 and Figure 4.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

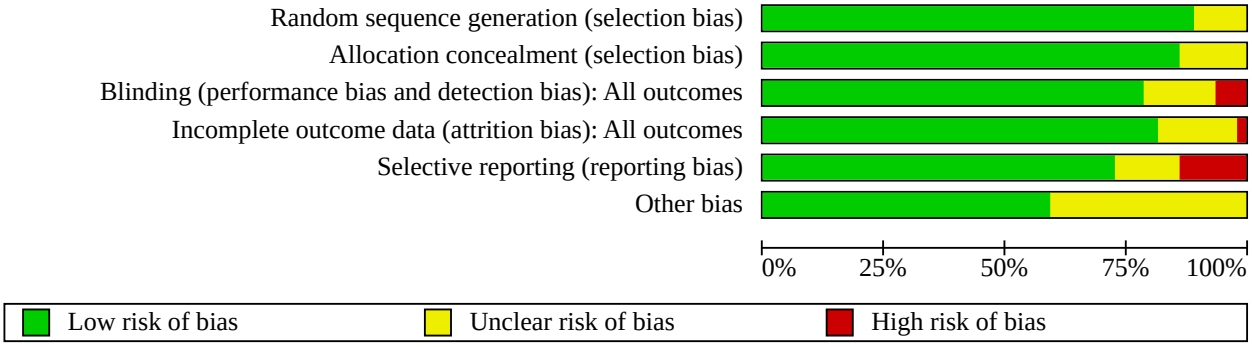


Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

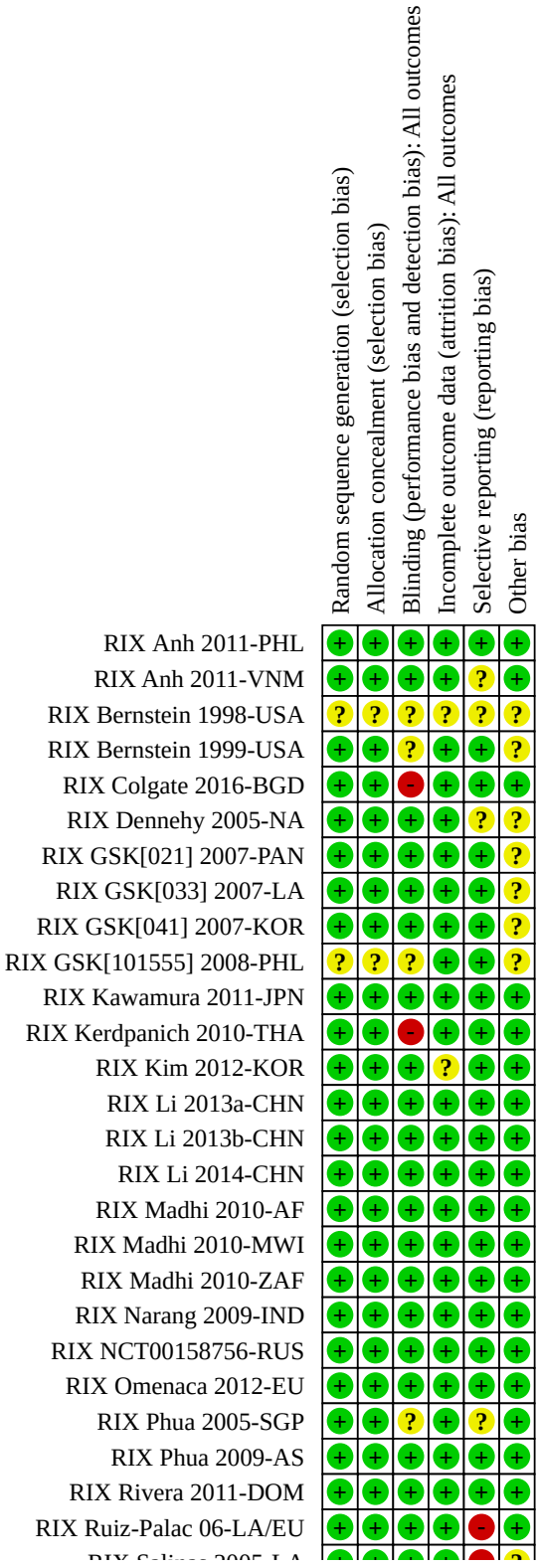
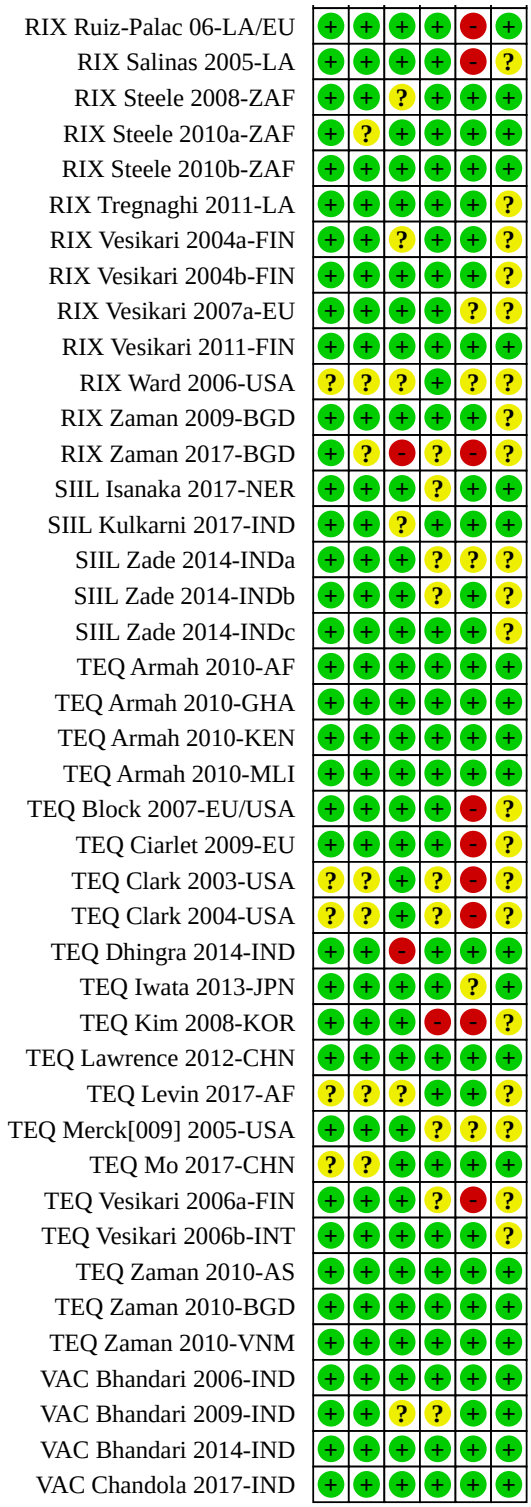


Figure 4. (Continued)



Detailed clinical study reports of most of the GlaxoSmithKline-sponsored studies (27 of the 36 Rotarix trials) have been published online (gsk-clinicalstudyregister.com). Full details of blinding, participant selection, and attrition are available from these reports and, for the 2019 update of this review, we could subsequently update risks of bias for these studies, where previously there was no information available.

Based on unpublished information provided by Merck, many of the RotaTeq trials' risks of bias were upgraded for the 2012 version of this review. Details of the unpublished information are indicated in the risk of bias tables in the Characteristics of included studies section.

Allocation

Of the 60 RCTs analysed in this review, 53 (88%) reported an adequate generation of allocation sequence, while the method of assignment was unclear in the remaining studies due to insufficient reporting. We considered the methods used to conceal allocation to be adequate in 51 trials (85%), and unclear in the remaining studies, again, due to insufficient reporting.

Blinding

Information about blinding of participants, care providers, and outcome assessors was provided and we considered blinding to be adequate in 46 studies (77%), unclear in ten studies due to insufficient reporting, and at high risk of bias in four studies: RIX Colgate 2016-BGD did not include a placebo arm and compared vaccine to no intervention, RIX Kerdpanich 2010-THA and TEQ Dhingra 2014-IND were single-blind studies, and RIX Zaman 2017-BGD was an open-label trial.

Incomplete outcome data

Incomplete outcome data were adequately addressed, or there were very little or no missing data in 48 studies (80%). In 11 studies, attrition bias was considered unclear, mainly due to insufficient reporting. In one study (TEQ Kim 2008-KOR), the risk of attrition bias was assessed as high because the reasons for missing data were related to the outcome.

Selective reporting

Forty-two (70%) trials were free from selective reporting bias, nine were not, and the remaining nine trials were unclear mainly due to insufficient information. High-risk assessments of reporting bias were due to incomplete reporting of more than one important outcome (TEQ Clark 2004-USA; TEQ Vesikari 2006a-FIN), key expected outcomes were not included (RIX Ruiz-Palac 06-LA/EU; RIX Zaman 2017-BGD; TEQ Kim 2008-KOR), or important prespecified outcomes were not reported (RIX Salinas 2005-LA; TEQ Block 2007-EU/USA; TEQ Ciarlet 2009-EU; TEQ Clark 2003-USA).

Other potential sources of bias

No other bias was apparent in 33 trials (55%). Other bias was unclear in the remaining 27 trials (45%), mainly due to limited reporting where other bias could not be ruled out.

Effects of interventions

See: **Summary of findings 1** Rotarix compared with placebo for preventing rotavirus diarrhoea in low-mortality countries; **Summary of findings 2** Rotarix compared with placebo for preventing rotavirus diarrhoea in medium-mortality countries; **Summary of findings 3** Rotarix compared with placebo for preventing rotavirus diarrhoea in high-mortality countries; **Summary of findings 4** RotaTeq compared with placebo for preventing rotavirus diarrhoea in low-mortality countries; **Summary of findings 5** RotaTeq compared with placebo for preventing rotavirus diarrhoea in medium-mortality countries; **Summary of findings 6** RotaTeq compared with placebo for preventing rotavirus diarrhoea in high-mortality countries; **Summary of findings 7** Rotasiil compared with placebo for preventing rotavirus diarrhoea in high-mortality countries; **Summary of findings 8** Rotavac compared with placebo for preventing rotavirus diarrhoea in high-mortality countries

1. Rotarix

1.1. Primary outcomes

Summary of findings of primary outcomes according to country mortality rate are presented in Summary of findings 1 (Rotarix, low-mortality countries), Summary of findings 2 (Rotarix, medium-mortality countries), and in Summary of findings 3 (Rotarix, high-mortality countries).

1.1.1. Rotavirus diarrhoea: severe

Fourteen trials provided data on the efficacy of Rotarix to prevent severe rotavirus diarrhoea in children; see Analysis 1.1 for up to one-year follow-up, Analysis 1.2 for second year of life data, and Analysis 1.3 for two years follow-up. Trials were performed in low-mortality countries (RIX Bernstein 1999-USA; RIX Kawamura 2011-JPN; RIX Phua 2005-SGP; RIX Phua 2009-AS; RIX Vesikari 2004b-FIN; RIX Vesikari 2007a-EU), medium-mortality countries (RIX Li 2014-CHN; RIX Ruiz-Palac 06-LA/EU; RIX Salinas 2005-LA; RIX Tregnaghi 2011-LA), and high-mortality countries (RIX Colgate 2016-BGD; RIX Madhi 2010-MWI; RIX Madhi 2010-ZAF; RIX Steele 2010b-ZAF; RIX Zaman 2017-BGD). Data below are grouped accordingly.

Low-mortality countries

Rotarix reduced severe rotavirus diarrhoea cases by 93% after one year (RR 0.07, 95% CI 0.03 to 0.18; 14,976 participants, 4 trials), by 87% in the second year of life (RR 0.13, 95% CI 0.08 to 0.20; 14,808 participants, 4 trials), and by 90% after two years (RR 0.10, 95% CI 0.07 to 0.14; 18,145 participants, 6 trials). After three years, the pooled estimate from two studies showed an effect in favour of Rotarix compared to placebo, but the 95% CIs were very wide (RR 0.10, 95% CI 0.01 to 1.52; 12,109 participants, RIX Phua 2009-AS and RIX Vesikari 2007a-EU; data not shown). Pooled results showed statistical heterogeneity at three years follow-up (I^2 = 69%, data not shown).

Medium-mortality countries

Rotarix reduced severe rotavirus diarrhoea cases by 79% during the first year of follow-up (RR 0.21, 95% CI 0.16 to 0.29; 31,671 participants, 4 trials), by 76% in the second year of life (RR 0.24, 95% CI 0.17 to 0.35; 17,733 participants, 3 trials), and by 78% after two years (RR 0.23, 95% CI 0.17 to 0.29; 23,834 participants, 3 trials).

High-mortality countries

Rotarix reduced severe rotavirus diarrhoea cases by 58% during the first year of follow-up (RR 0.42, 95% CI 0.28 to 0.61; 9951 participants, 5 comparisons from 4 trials), made little or no difference in the second year of life (RR 0.82, 95% CI 0.52 to 1.29; 6049 participants, 3 comparisons from 2 trials), and reduced severe rotavirus diarrhoea cases by 35% after two years (RR 0.65, 95% CI 0.51 to 0.83; 7113 participants, 3 comparisons from 2 trials). Pooled results showed statistical heterogeneity at one-year follow-up (I^2 = 52%, Analysis 1.1).

1.1.2. All-cause diarrhoea: severe

Severe all-cause diarrhoea was reported as cases in seven trials (RIX Colgate 2016-BGD; RIX Li 2014-CHN; RIX Madhi 2010-AF; RIX Phua 2005-SGP; RIX Ruiz-Palac 06-LA/EU; RIX Tregnaghi 2011-LA; RIX Vesikari 2007a-EU) and as episodes in two trials (RIX Phua 2009-AS; RIX Ruiz-Palac 06-LA/EU). We have reported these data separately. Trials were performed in low-mortality countries (RIX Phua 2005-SGP; RIX Phua 2009-AS; RIX Vesikari 2007a-EU), medium-mortality countries (RIX Li 2014-CHN; RIX Ruiz-Palac 06-LA/EU; RIX Tregnaghi 2011-LA), and in high-mortality countries (RIX Colgate 2016-BGD; RIX Madhi 2010-MWI; RIX Madhi 2010-ZAF).

Low-mortality countries

Rotarix reduced the number of severe cases of all-cause diarrhoea by 52% at one year (RR 0.48, 95% CI 0.37 to 0.61; 3874 participants, 1 trial; Analysis 1.4), and by 51% at two years (RR 0.49, 95% CI 0.40 to 0.60; 6269 participants, 2 trials; Analysis 1.5). Rotarix reduced the rate of severe episodes of all-cause diarrhoea by 30% at two years (rate ratio 0.70, 95% CI 0.56 to 0.86; 39,091 participants, 1 trial; Analysis 1.7). One trial reported on severe all-cause diarrhoea after three years follow-up (RIX Phua 2009-AS); Rotarix reduced the number of severe cases by 27% (RR 0.73, 95% CI 0.61 to 0.88; 10,519 participants; data not shown).

Medium-mortality countries

Rotarix reduced the number of severe cases of all-cause diarrhoea by 36% at one year (RR 0.64, 95% CI 0.52 to 0.79; 26,479 participants, 2 trials; Analysis 1.4), and by 26% at two years (RR 0.74, 95% CI 0.50 to 1.09; 23,317 participants, 2 trials; Analysis 1.5). Pooled results showed statistical heterogeneity at both one year (I^2 = 46%) and two years follow-up (I^2 = 92%). Rotarix reduced the rate of severe episodes of all-cause diarrhoea by 40% at one year (rate ratio 0.60, 95% CI 0.50 to 0.72; 17,867 participants, 1 trial; Analysis 1.6), and by 39% at two years (rate ratio 0.61, 95% CI 0.53 to 0.70; 39,091 participants, 1 trial; Analysis 1.7).

High-mortality countries

Rotarix reduced the number of severe cases of all-cause diarrhoea by 27% at one-year follow-up (RR 0.73, 95% CI 0.56 to 0.95; 5639 participants, 3 comparisons from 2 trials; Analysis 1.4), and by 17% at two years follow-up (RR 0.83, 95% CI 0.72 to 0.96; 2764 participants, 2 comparisons from 1 trial; Analysis 1.5). Pooled results showed statistical heterogeneity at one-year follow-up (I^2 = 75%).

1.1.3. All-cause death

Thirty trials reported on all-cause death, either as the number of deaths (RIX Bernstein 1999-USA; RIX Kim 2012-KOR; RIX Li 2013b-CHN; RIX Li 2014-CHN; RIX Madhi 2010-AF; RIX NCT00158756-RUS; RIX Phua 2005-SGP; RIX Phua 2009-AS; RIX Steele 2010a-ZAF; RIX Vesikari 2007a-EU) or as the number of fatal serious adverse events (RIX Anh 2011-PHL; RIX Anh 2011-VNM; RIX GSK[021] 2007-PAN; RIX GSK[033] 2007-LA; RIX GSK[041] 2007-KOR; RIX GSK[101555] 2008-PHL; RIX Kawamura 2011-JPN; RIX Kerdpanich 2010-THA; RIX Narang 2009-IND; RIX Omenaca 2012-EU; RIX Rivera 2011-DOM; RIX Ruiz-Palac 06-LA/EU; RIX Salinas 2005-LA; RIX Steele 2008-ZAF; RIX Steele 2010b-ZAF; RIX Tregnaghi 2011-LA; RIX Vesikari 2004b-FIN; RIX Vesikari 2011-FIN; RIX Zaman 2009-BGD). We pooled the number of deaths and fatal serious adverse events; see Analysis 1.8. We present details of causes of death for each trial in Appendix 7. Ten trials were performed in low-mortality countries, nine trials in medium-mortality countries, and 11 trials in high-mortality countries.

Low-mortality countries

There was little or no difference in all-cause death between infants and children that received Rotarix or placebo (RR 0.71, 95% CI 0.17 to 2.88; 20,361 participants, 10 trials; Analysis 1.8). Five deaths occurred among 12,018 participants in the Rotarix arms and four deaths occurred among 8343 participants in the placebo arms. This corresponds to a risk difference of 14 fewer deaths with Rotarix per 100,000 with the 95% CI indicating from 40 fewer to 90 more per 100,000 (data not shown).

Medium-mortality countries

There was little or no difference in all-cause death between infants and children that received Rotarix or placebo (RR 1.27, 95% CI 0.89 to 1.81; 77,043 participants, 10 trials; Analysis 1.8). Seventy-seven deaths occurred among 40,821 participants in the Rotarix arms and 53 deaths occurred among 36,222 participants in the placebo arms. This corresponds to a risk difference of 40 more deaths with Rotarix per 100,000 with the 95% CI indicating from 16 fewer to 119 more per 100,000 (data not shown).

High-mortality countries

There was no little or no difference in all-cause death between the two arms (RR 0.88, 95% CI 0.63 to 1.21; 8374 participants, 8 trials). Ninety-eight deaths occurred among 5519 participants in the Rotarix arms and 58 deaths occurred among 2855 participants in the placebo arms. This corresponds to a risk difference of 244 fewer deaths with Rotarix per 100,000 with the 95% CI indicating from 752 fewer to 427 more per 100,000 (data not shown).

1.1.4. All serious adverse events

The total number of serious adverse events was reported in 31 trials, performed in low-mortality countries (RIX Bernstein 1998-USA; RIX Dennehy 2005-NA; RIX GSK[041] 2007-KOR; RIX Kawamura 2011-JPN; RIX Kim 2012-KOR; RIX Omenaca 2012-EU; RIX Phua 2005-SGP; RIX Phua 2009-AS; RIX Vesikari 2004a-FIN; RIX Vesikari 2004b-FIN; RIX Vesikari 2007a-EU; RIX Vesikari 2011-FIN), medium-mortality countries (RIX GSK[021] 2007-PAN; RIX GSK[033] 2007-LA; RIX Kerdpanich 2010-THA; RIX Li 2013b-CHN; RIX Li 2014-CHN; RIX NCT00158756-RUS; RIX Ruiz-Palac 06-LA/EU; RIX Salinas 2005-LA; RIX Tregnaghi 2011-LA), and in high-mortality countries (RIX Anh 2011-PHL; RIX Anh 2011-VNM; RIX GSK[101555] 2008-PHL; RIX Madhi 2010-AF; RIX Narang 2009-IND; RIX Rivera 2011-DOM; RIX Steele 2008-ZAF; RIX Steele 2010a-ZAF; RIX Steele 2010b-ZAF; RIX Zaman 2009-BGD); see Analysis 1.9.

Low-mortality countries

There was little or no difference between children allocated to Rotarix compared with placebo in the risk of serious adverse events (RR 0.89, 95% CI 0.72 to 1.10; 18,971 participants, 12 trials).

Medium-mortality countries

Fewer children allocated to Rotarix had serious adverse events compared with placebo (RR 0.85, 95% CI 0.76 to 0.95; 77,069 participants, 9 trials). In addition, in one trial (RIX Li 2013a-CHN) that vaccinated 25 older children (aged two to six years) with one-dose Rotarix, there were no serious adverse events reported.

High-mortality countries

There was little or no difference in the number of serious adverse events between the two arms (RR 0.90, 95% CI 0.77 to 1.05; 7674 participants, 10 trials).

1.1.5. Serious adverse events: intussusception

Twenty-one trials reported on intussusception, and 11 of these reported that no cases of intussusception had occurred. Trials were performed in low-mortality countries (RIX Dennehy 2005-NA; RIX GSK[041] 2007-KOR; RIX Kawamura 2011-JPN; RIX Kim 2012-KOR; RIX Phua 2005-SGP; RIX Phua 2009-AS;RIX Vesikari 2004b-FIN; RIX Vesikari 2007a-EU; RIX Vesikari 2011-FIN), in medium-mortality countries (RIX Ruiz-Palac 06-LA/EU; RIX Salinas 2005-LA; RIX Tregnaghi 2011-LA), and in high-mortality countries (RIX Madhi 2010-AF; RIX Rivera 2011-DOM; RIX Steele 2008-ZAF; RIX Steele 2010b-ZAF; RIX Zaman 2017-BGD); see Analysis 1.10.

Low-mortality countries

Eleven cases of intussusception were reported in a total of 12,399 children in the Rotarix arm compared with six cases of intussusception in 8374 children of the placebo arm. Pooled results showed no increased risk for intussusception in children receiving Rotarix when compared to placebo (RR 1.42, 95% CI 0.52 to 3.87; 20,773 participants, 10 trials).

Medium-mortality countries

Twenty cases of intussusception were reported in a total of 39,519 children in the Rotarix arm compared with 23 cases of intussusception in 36,021 children of the placebo arm. Pooled results showed no increased risk for intussusception in children receiving Rotarix when compared to placebo (RR 0.72, 95% CI 0.39 to 1.32; 75,540 participants, 6 trials).

High-mortality countries

One case of intussusception was reported in a total of 6384 children in the Rotarix arm compared with no cases of intussusception in 4276 children in the placebo or no-intervention arm. Pooled results showed no increased risk for intussusception in children receiving Rotarix when compared to placebo (RR 1.49, 95% CI 0.06 to 36.63; 10,660 participants, 5 trials).

1.2. Secondary outcomes

1.2.1 Serious adverse events: Kawasaki disease

Three trials reported four cases of Kawasaki disease among 7701 children allocated to Rotarix compared to no cases in 5416 children allocated to placebo (RIX Phua 2005-SGP; RIX Phua 2009-AS; RIX Salinas 2005-LA). We did not observe a statistically significant difference between the intervention and placebo groups (RR 1.75, 95% CI 0.29 to 10.73; 13,117 participants, 3 trials; Analysis 1.11).

1.2.2. Serious adverse events requiring hospitalization

Two trials reported serious adverse events requiring hospitalization (RIX Ruiz-Palac 06-LA/EU; RIX Steele 2008-ZAF) and found fewer events in the Rotarix group than the placebo group (RR 0.88, 95% CI 0.81 to 0.96; 63,675 participants, 2 trials; Analysis 1.12).

1.2.3 Rotavirus diarrhoea of any severity

Eighteen trials provided data for the efficacy of Rotarix to prevent rotavirus diarrhoea of any severity in children; see Analysis 1.13 for two-month safety trial follow-up, Analysis 1.14 for one-year follow-up and Analysis 1.16 for two-year follow-up. Trials were performed in low-mortality countries (RIX Bernstein 1999-USA; RIX GSK[041] 2007-KOR; RIX Omenaca 2012-EU; RIX Phua 2005-SGP; RIX Vesikari 2004b-FIN; RIX Vesikari 2007a-EU; RIX Vesikari 2011-FIN), medium-mortality countries (RIX Kerdpanich 2010-THA; RIX Salinas 2005-LA), and in high-mortality countries (RIX Anh 2011-PHL; RIX Anh 2011-VNM; RIX GSK[101555] 2008-PHL; RIX Madhi 2010-MWI; RIX Madhi 2010-ZAF; RIX Narang 2009-IND; RIX Rivera 2011-DOM; RIX Steele 2010a-ZAF; RIX Steele 2010b-ZAF; RIX Zaman 2009-BGD). Data below are grouped accordingly.

Low-mortality countries

Safety trials (up to two months follow-up): Rotarix was not superior to placebo in the prevention of rotavirus diarrhoea in the trials assessing outcomes up to two months after vaccination (RR 0.88, 95% CI 0.23 to 3.32; 2061 participants, 4 trials). These trials, although reporting cases of rotavirus diarrhoea, were not designed to measure efficacy.

Efficacy trials (one to three years follow-up): Rotarix reduced rotavirus diarrhoea by 85% at up to one year (RR 0.15, 95% CI 0.10 to 0.24; 4457 participants, 3 trials) and 78% at up to two years of follow-up (RR 0.22, 95% CI 0.18 to 0.27; 6878 participants, 4 trials). At the third year of follow-up, there were very few reported cases of rotavirus diarrhoea of any severity. Based on a single trial (RIX Vesikari 2007a-EU, 1590 participants), there was no difference between Rotarix and placebo groups (data not shown).

Medium-mortality countries

Safety trials (up to two months follow-up): Rotarix was not superior to placebo in the prevention of rotavirus diarrhoea in the trials assessing outcomes up to two months after vaccination (RR 1.21, 95% CI 0.07 to 22.23; 444 participants, 1 trial). This trial, although reporting cases of rotavirus diarrhoea, was not designed to measure efficacy.

Efficacy trials (one to two years follow-up): Rotarix reduced rotavirus diarrhoea by 66% at up to one year (RR 0.34, 95% CI 0.26 to 0.44; 5192 participants, 2 trials) and 54% at up to two years of follow-up (RR 0.46, 95% CI 0.35 to 0.59; 3665 participants, 2 trials).

High-mortality countries

Safety trials (up to two months follow-up): Three trials found no difference in the Rotarix group compared to placebo when outcomes were assessed up to two months after vaccination (RR 1.21, 95% CI 0.65 to 2.22; 1789 participants, 7 trials).

Efficacy trials (one to two years follow-up): Rotarix reduced rotavirus diarrhoea by 49% during the first year of follow-up (RR 0.51, 95% CI 0.39 to 0.68; 9951 participants, 5 comparisons from 4 trials), and by 45% at up to two years follow-up (RR 0.55, 95% CI 0.32 to 0.93; 5600 participants, 2 trials). Pooled results showed statistical heterogeneity at one-year follow-up (I^2 = 70%, Analysis 1.14) and at up to two years follow-up (I^2 = 77%, Analysis 1.16).

1.2.4. All-cause diarrhoea: of any severity

This outcome was reported as cases in five trials from low-mortality countries (RIX Kim 2012-KOR; RIX Omenaca 2012-EU; RIX Phua 2005-SGP; RIX Vesikari 2004b-FIN; RIX Vesikari 2011-FIN), in four trials from medium-mortality countries (RIX Kerdpanich 2010-THA;

RIX Li 2014-CHN; RIX Rivera 2011-DOM; RIX Salinas 2005-LA), and in four trials from high-mortality countries (RIX Anh 2011-PHL; RIX Anh 2011-VNM; RIX Colgate 2016-BGD; RIX Steele 2010a-ZAF). All-cause diarrhoea of any severity was reported as episodes in one trial from low-mortality countries (RIX Vesikari 2004b-FIN) and in two trials from medium-mortality countries (RIX Rivera 2011-DOM; RIX Salinas 2005-LA). We have reported on cases and episodes separately.

Low-mortality countries

Safety trials (up to two months follow-up): Rotarix was not better than placebo in reducing the number of cases of all-cause diarrhoea at two months follow-up (RR 0.80, 95% CI 0.59 to 1.08; 1906 participants, 3 trials; Analysis 1.17).

Efficacy trials (two years follow-up): Rotarix was not better than placebo in reducing the number of cases of all-cause diarrhoea at two years follow-up (RR 0.81, 95% CI 0.65 to 1.00; 2789 participants, 2 trials, Analysis 1.19). One trial reported the number of episodes, with little or no difference with Rotarix when compared to placebo at up to two years follow-up (rate ratio 1.02, 95% CI 0.78 to 1.33; 736 participants, 1 trial; Analysis 1.21).

Medium-mortality countries

Safety trials (up to two months follow-up): Rotarix was not better than placebo in reducing the number of cases of all-cause diarrhoea at two months follow-up (RR 0.97, 95% CI 0.46 to 2.02; 444 participants, 1 trial; Analysis 1.17).

Efficacy trials (one to two years follow-up): Rotarix was slightly better than placebo in reducing the number of cases of all-cause diarrhoea at one-year follow-up (RR 0.89, 95% CI 0.80 to 0.98; 2244 participants, 2 trials, Analysis 1.18), and there was little or no difference at up to two years follow-up (RR 0.95, 95% CI 0.90 to 1.01; 3665 participants, 2 trials; Analysis 1.19). Two trials reported the number of episodes, with little or no difference with Rotarix when compared to placebo at one year (rate ratio 0.98, 95% CI 0.88 to 1.10; 2204 participants, 2 trials; Analysis 1.20).

High-mortality countries

Safety trials (up to two months follow-up): Rotarix was not better than placebo in reducing the number of cases of all-cause diarrhoea at two months follow-up (RR 1.01, 95% CI 0.74 to 1.38; 3132 participants, 3 trials; Analysis 1.17).

Efficacy trials (one-year follow-up): Rotarix was not better than no intervention in reducing the number of cases of all-cause diarrhoea at one-year follow-up (RR 0.99, 95% CI 0.93 to 1.05; 700 participants, 1 trial; Analysis 1.18).

1.2.5. All-cause hospitalizations

Two trials (RIX Phua 2005-SGP; RIX Ruiz-Palac 06-LA/EU) provided data for the efficacy of Rotarix to prevent all-cause hospitalizations.

Low-mortality countries

Rotarix reduced the number of all-cause hospitalizations by 64% at up to two years of follow-up (RR 0.36, 95% CI 0.15 to 0.86; 2421 participants, 1 trial; Analysis 1.22).

Medium-mortality countries

Rotarix slightly reduced the number of all-cause hospitalizations at up to two years of follow-up (RR 0.88, 95% CI 0.81 to 0.96; 63,225 participants, 1 trial; Analysis 1.22).

1.2.6. Rotavirus diarrhoea: requiring hospitalization or medical attention

Rotavirus-related hospitalizations were reduced by 82% after one year (RR 0.18, 95% CI 0.09 to 0.33; 48,718 participants, 8 trials), 85% at two years (RR 0.15, 95% CI 0.11 to 0.22; 35,331 participants, 7 trials), and 95% at three years (RR 0.05, 95% CI 0.02 to 0.16; 10,519 participants, 1 trial (RIX Phua 2009-AS, data not shown); pooled results showed statistical heterogeneity at one year of follow-up (I^2 = 55%); see Analysis 1.23.

Rotarix reduced rotavirus-related medical visits by 92% at one year (RR 0.08, 95% CI 0.04 to 0.16; 3874 participants, 1 trial) and 78% at two years (RR 0.22, 95% CI 0.16 to 0.31; 7017 participants, 3 trials); see Analysis 1.24.

1.2.7. All-cause diarrhoea: requiring hospitalization

Rotarix reduced cases of hospitalization for all-cause diarrhoea at one-year follow-up by 46% (RR 0.54, 95% CI 0.35 to 0.83; 20,703 participants, 3 trials; Analysis 1.25). At two years follow-up, Rotarix reduced cases by 48% (RR 0.52, 95% CI 0.27 to 0.99; 14,367 participants, 2 trials; Analysis 1.25). RIX Phua 2009-AS reported that for hospitalizations due to all-cause diarrhoea at three years of follow-up, Rotarix reduced hospitalizations by 28% (RR 0.72, 95% CI 0.59 to 0.86; 10,519 participants, data not shown). Pooled results showed statistical heterogeneity at one-year (I^2 = 68%) and at two years follow-up (I^2 = 77%).

RIX Ruiz-Palac 06-LA/EU presented data on the number of episodes (Analysis 1.26); Rotarix reduced hospitalization all-cause diarrhoea episodes by 42% at one year (rate ratio 0.58, 95% CI 0.47 to 0.71; 17,867 participants, 1 trial) and 47% at two years (rate ratio 0.53, 95% CI 0.46 to 0.61; 14,286 participants, 1 trial).

1.2.8. Reactogenicity

The occurrence of fever (Analysis 1.27), diarrhoea (Analysis 1.28), and vomiting (Analysis 1.29) were evaluated at several time points: after the first dose, after the second dose, after the third dose, and at the end of the follow-up period. Most trials contributed data to these outcomes. There were similar results for Rotarix and placebo for each outcome and time point.

1.2.9. Adverse events that require discontinuation of vaccination schedule

There was little or no difference detected between Rotarix and placebo in the number of adverse events leading to discontinuation of the vaccination schedule (RR 1.01, 95% CI 0.82 to 1.25; 94,980 participants, 26 trials; Analysis 1.30).

1.3. Dropouts before the end of trial

Twenty-eight trials reported on the number of participants who dropped out of the trial before it ended. Overall, there were slightly fewer dropouts from the Rotarix compared with the placebo or no-intervention groups (RR 0.94, 95% CI 0.90 to 0.99; 93,106 participants, 28 trials; Analysis 1.31).

1.4. Subgroup analyses

1.4.1. Rotavirus serotype (G- or P-type)

Rotavirus diarrhoea: of any severity

Seven trials reported on rotavirus diarrhoea of any severity by different G types. There were fewer cases of rotavirus diarrhoea of any severity in the group receiving Rotarix when compared to placebo, regardless of G type (G1, G2, G3, G4, G9, G12); however, the pooled data for G1 (I^2 = 81%) and G9 (I^2 = 25%) types showed statistical heterogeneity, see Analysis 1.32.

Three trials reported on rotavirus diarrhoea of any severity by different P types. There were fewer cases of rotavirus diarrhoea of any severity in the group receiving Rotarix when compared to placebo for P8. The results were inconclusive for P4 and P6 due to very few events leading to a very wide 95% CI. The pooled data for P8 type showed statistical heterogeneity (I^2 = 67%), see Analysis 1.32.

Rotavirus diarrhoea: severe

There were fewer severe cases of rotavirus diarrhoea in the Rotarix groups compared with placebo in cases attributed to the G1, G2, G3, G4, G9, G12, P4, P6, and P8 types; see Analysis 1.33. Results were inconclusive for G8 types due to few reported cases leading to a very wide 95% CI. The pooled data for G1, G4, G8 and P8 types showed statistical heterogeneity (I^2 = 65% (G1), 51% (G4), 63% (G8), 65% (P8)).

1.4.2. Malnourished children

Rotavirus diarrhoea: of any severity

One trial provided data separately as the number of cases of rotavirus diarrhoea of any severity in a subgroup of malnourished children (RIX Salinas 2005-LA). Rotarix was significantly better than placebo in preventing rotavirus diarrhoea for this subgroup at one year of follow-up (RR 0.39, 95% CI 0.19 to 0.79; 287 participants, 1 trial, Analysis 1.34).

1.4.3. Children infected with HIV

Rotavirus diarrhoea: of any severity

One safety trial included only confirmed HIV-positive, asymptomatic or mildly symptomatic children (RIX Steele 2010a-ZAF). At one-month follow-up, little or no difference between the Rotarix and placebo arms for rotavirus diarrhoea was reported (RR 1.00, 95% CI 0.26 to 3.78; 100 participants, 1 trial; Analysis 1.35).

One efficacy trial included children who were infected with HIV or children that had been exposed to HIV, as long as they were not clinically immunosuppressed (e.g. AIDS) at the age of vaccination (six weeks) (RIX Madhi 2010-AF). HIV tests were performed on approximately 46% of children from Malawi and 23% of children from South Africa. We did not conduct a specific analysis for this population, but the authors stated that demographic characteristics and the proportion of children who were infected with HIV were similar across the study groups.

1.5 Sensitivity analysis

1.5.1 Primary outcomes with high heterogeneity according to allocation concealment

To investigate heterogeneity for primary outcomes with pooled results where I^2 > 75%, we planned to pool data only from studies with low risk of bias for allocation concealment in a sensitivity analysis. We rated all trials at low risk of bias for allocation concealment for the two outcomes where heterogeneity was high (I^2 > 75%); see Analysis 1.4 (I^2 = 75%) and Analysis 1.5 (I^2 = 92%).

1.5.2 Cluster-randomized trials

Three outcomes (serious adverse events: intussusception, rotavirus severe diarrhoea, and rotavirus diarrhoea of any severity at one and two years follow-up) included one cluster-randomized trial carried out in a high-mortality country (RIX Zaman 2017-BGD). When we excluded data from this trial, there was a small but non-significant change to the effect estimate and 95% CI for rotavirus diarrhoea: severe at up to one-year follow-up (from RR 0.42, 95% CI 0.28 to 0.61; 9951 participants, 5 comparisons from 4 trials (Analysis 1.1) to RR 0.37, 95% CI 0.23 to 0.60, 6114 participants, 4 comparisons in 3 trials (analysis not shown)); in the second year of life (from RR 0.82, 95% CI 0.52 to 1.29; 6049 participants, 3 comparisons from 2 trials (Analysis 1.2) to RR 0.78, 95% CI 0.46 to 1.33, 2212 participants, 2 comparisons in 1 trial (analysis not shown)); and at up to 2 years follow-up (from RR 0.65, 95% CI 0.51 to 0.83; 7113 participants, 3 comparisons from 2 trials (Analysis 1.3) to RR 0.58, 95% CI 0.42 to 0.79, 2764 participants, 2 comparisons in 1 trial (analysis not shown)). There was also a small but non-significant change to the effect estimate and 95% CI for rotavirus diarrhoea of any severity at up to one-year follow-up (from RR 0.51, 95% CI 0.39 to 0.68; 9951 participants, 5 comparisons from 4 trials (Analysis 1.14) to RR 0.49, 95% CI 0.35 to 0.68, 6114 participants, 4 comparisons in 3 trials (analysis not shown)); in the second year of life (from RR 0.66, 95% CI 0.36 to 1.18, 4855 participants, 2 trials (Analysis 1.15) to RR 0.48, 95% CI 0.19 to 1.21, 1018 participants, 1 trial (analysis not shown)); and at up to 2 years follow-up (from RR 0.55, 95% CI 0.32 to 0.93; 5600 participants, 2 trials (Analysis 1.16) to RR 0.41, 95% CI 0.28 to 0.62, 1251 participants, 1 trial (analysis not shown)). There were no changes to effect estimates or 95% CIs for serious adverse events: intussusception.

2. RotaTeq

2.1. Primary outcomes

Summary of findings of primary outcomes according to country mortality rate are presented in Summary of findings 4 (RotaTeq, low-mortality countries), Summary of findings 5 (RotaTeq, medium-mortality countries), and in Summary of findings 6 (RotaTeq, high-mortality countries).

2.1.1. Rotavirus diarrhoea: severe

Seven trials provided data for the efficacy of RotaTeq to prevent severe rotavirus diarrhoea in children; see Analysis 2.1 for up to one-year follow-up, Analysis 2.2 for second year of life data, and Analysis 2.3 for two years follow-up. Trials were performed in low-mortality countries (TEQ Clark 2004-USA; TEQ Vesikari 2006a-FIN; TEQ Vesikari 2006b-INT; TEQ Block 2007-EU/USA; TEQ Iwata 2013-JPN), one trial in a medium-mortality country (TEQ Mo 2017-CHN), and two trials were split between five high-mortality countries (TEQ Zaman 2010-VNM; TEQ Zaman 2010-BGD; TEQ Armah 2010-GHA;

TEQ Armah 2010-MLI; TEQ Armah 2010-KEN). Data below are grouped accordingly.

Low-mortality countries

RotaTeq reduced the number of severe rotavirus diarrhoea cases by 97% at one year (RR 0.03, 95% CI 0.01 to 0.11; 7688 participants, 5 trials), by 91% in the second year of life (RR 0.09, 95% CI 0.02 to 0.33; 2596 participants, 2 trials), and by 96% by two years (RR 0.04, 95% CI 0.01 to 0.11; 5442 participants, 2 trials).

Medium-mortality countries

RotaTeq reduced the number of severe rotavirus diarrhoea cases by 79% at two years (RR 0.21, 95% CI 0.11 to 0.41; 1937 participants, 1 trial).

High-mortality countries

RotaTeq reduced the number of severe rotavirus diarrhoea cases by 57% at one year (RR 0.43, 95% CI 0.29 to 0.64; 6775 participants, 5 comparisons from 2 trials), by 26% in the second year of life (RR 0.74, 95% CI 0.55 to 0.99; 6081 participants, 5 comparisons from 2 trials), and by 44% at two years (RR 0.56, 95% CI 0.41 to 0.77; 6744 participants, 5 comparisons from 2 trials). Pooled results showed statistical heterogeneity at two-year follow-up (I^2 = 41%); see Analysis 2.3.

2.1.2. All-cause diarrhoea: severe

Only two trials provided data for the efficacy of RotaTeq to prevent severe all-cause diarrhoea in children; see Analysis 2.4 for one-year follow-up and Analysis 2.5 for two-year follow-up. Trials were performed in high-mortality countries and one trial was split by country (TEQ Armah 2010-GHA; TEQ Armah 2010-KEN; TEQ Armah 2010-MLI; TEQ Zaman 2010-AS). We did not identify any trial that reported on this outcome that was performed in a low- or medium-mortality country.

High-mortality countries

There was little or no difference between RotaTeq and placebo for all-cause severe diarrhoea at one-year follow-up (RR 0.80, 95% CI 0.58 to 1.11; 4085 participants, 3 comparisons from 1 trial). At two-year follow-up, RotaTeq reduced severe cases by 15% (RR 0.85, 95% CI 0.74 to 0.99; 5977 participants, 4 comparisons from 2 trials). Pooled results showed statistical heterogeneity at one-year follow-up (I^2 = 46%); see Analysis 2.4.

2.1.3. All-cause death

Eleven trials reported on all-cause death, in most trials as the number of deaths (TEQ Armah 2010-AF; TEQ Iwata 2013-JPN; TEQ Lawrence 2012-CHN; TEQ Levin 2017-AF; TEQ Merck[009] 2005-USA; TEQ Mo 2017-CHN; TEQ Vesikari 2006a-FIN; TEQ Vesikari 2006b-INT; TEQ Zaman 2010-AS), and in two trials as fatal serious adverse events (TEQ Block 2007-EU/USA; TEQ Ciarlet 2009-EU). We pooled the number of deaths and fatal serious adverse events; see Analysis 2.6. We present details of causes of death for each trial in Appendix 7. Six trials were performed in low-mortality countries (TEQ Block 2007-EU/USA; TEQ Ciarlet 2009-EU; TEQ Iwata 2013-JPN; TEQ Merck[009] 2005-USA; TEQ Vesikari 2006a-FIN, TEQ Vesikari 2006b-INT), two trials in medium-mortality countries (TEQ Lawrence 2012-CHN; TEQ Mo 2017-CHN), and three trials were split between six high-mortality countries (TEQ Armah 2010-GHA; TEQ Armah 2010-KEN; TEQ Armah 2010-MLI; TEQ Levin 2017-AF; TEQ Zaman 2010-BGD; TEQ Zaman 2010-VNM).

Low-mortality countries

There was little or no difference in all-cause death between RotaTeq and placebo arms (RR 1.24, 95% CI 0.69 to 2.22; 72,654 participants, 6 trials). Twenty-five deaths occurred among 36,973 participants in the RotaTeq arms and 20 deaths occurred among 34,003 participants in the placebo arms. This corresponds to a risk difference of 13 more deaths with RotaTeq per 100,000 with the 95% CI indicating from 17 fewer to 68 more per 100,000 (data not shown).

Medium-mortality countries

The results for all-cause death in medium-mortality countries was inconclusive due to only one reported event leading to wide 95% CIs (RR 0.33, 95% CI 0.01 to 8.18; 4088 participants, 2 trials). No deaths occurred among 2044 participants in the RotaTeq arm and one death occurred among 2044 participants in the placebo arm. This corresponds to a risk difference of 33 fewer deaths with RotaTeq per 100,000 with the 95% CI indicating from 48 fewer to 351 more per 100,000 (data not shown).

High-mortality countries

There was little or no difference in all-cause death between the two arms (RR 0.91, 95% CI 0.68 to 1.23; 7706 participants, 6 comparisons from 4 trials). Eighty-eight deaths occurred among 42,867 participants in the RotaTeq arms and 88 deaths occurred among 41,581 participants in the placebo arms. This corresponds to a risk difference of 205 fewer deaths with RotaTeq per 100,000 with the 95% CI indicating from 730 fewer to 525 more per 100,000 (data not shown).

2.1.4. All serious adverse events

Serious adverse events were reported in 11 trials: in five trials in low-mortality countries (TEQ Block 2007-EU/USA; TEQ Ciarlet 2009-EU; TEQ Iwata 2013-JPN; TEQ Kim 2008-KOR; TEQ Vesikari 2006b-INT), in two trials in medium-mortality countries (TEQ Lawrence 2012-CHN; TEQ Mo 2017-CHN), and in four trials split into seven country-level comparisons in high-mortality countries (TEQ Armah 2010-GHA; TEQ Armah 2010-KEN; TEQ Armah 2010-MLI; TEQ Dhingra 2014-IND; TEQ Levin 2017-AF; TEQ Zaman 2010-BGD; TEQ Zaman 2010-VNM); see Analysis 2.7.

Low-mortality countries

There was little or no difference between children allocated to RotaTeq compared with placebo in serious adverse events (RR 0.92, 95% CI 0.84 to 1.01; 70,690 participants, 5 trials; Analysis 2.7).

Medium-mortality countries

Pooled results showed little or no difference in the number of serious adverse events in the RotaTeq group compared with the placebo group (RR 0.66, 95% CI 0.14 to 3.17; 4082 participants, 2 trials; Analysis 2.7) with statistical heterogeneity (I^2 = 42%). In addition, in a separate cohort of TEQ Lawrence 2012-CHN that vaccinated 24 older children (aged two to six years) with one-dose RotaTeq, there were no serious adverse events reported.

High-mortality countries

Pooled results showed little or no difference in the number of serious adverse events in the RotaTeq group compared with the placebo group (RR 0.99, 95% CI 0.72 to 1.36; 7730 participants, 7 comparisons from 4 trials; Analysis 2.7).

2.1.5. Serious adverse events: intussusception

Thirteen trials reported cases of intussusception. Trials were performed in nine low-mortality countries (TEQ Block 2007-EU/USA; TEQ Ciarlet 2009-EU; TEQ Clark 2003-USA; TEQ Clark 2004-USA; TEQ Iwata 2013-JPN; TEQ Kim 2008-KOR; TEQ Merck[009] 2005-USA; TEQ Vesikari 2006a-FIN; TEQ Vesikari 2006b-INT), two trials in medium-mortality countries (TEQ Lawrence 2012-CHN; TEQ Mo 2017-CHN), and two trials split into five country-level comparisons in high-mortality countries (TEQ Armah 2010-GHA; TEQ Armah 2010-KEN; TEQ Armah 2010-MLI; TEQ Zaman 2010-BGD; TEQ Zaman 2010-VNM); see Analysis 2.8.

Low-mortality countries

Fourteen cases of intussusception were reported in a total of 37,846 children in the RotaTeq arms compared with 19 cases of intussusception in 36,079 children in the placebo arms. This corresponds to a risk difference of 16 fewer cases of intussusception with RotaTeq per 100,000 children with the 95% CI indicating from 34 fewer to 20 more per 100,000 (data not shown). Pooled results showed no increased risk of intussusception in children receiving RotaTeq when compared to placebo (RR 0.69, 95% CI 0.35 to 1.38; 73,925 participants, 9 trials; Analysis 2.8).

Medium-mortality countries

Two cases of intussusception were reported in a total of 2039 children in the RotaTeq arms compared with no cases of intussusception in 2043 children in the placebo arms. Risk difference could not be estimated due to no events in the placebo arms. Pooled results showed no increased risk of intussusception in children receiving RotaTeq when compared to placebo (RR 5.01, 95% CI 0.24 to 104.29; 4082 participants, 2 trials; Analysis 2.8).

High-mortality countries

No cases of intussusception were reported in a total of 3744 children in the RotaTeq arms compared with one case of intussusception in 3744 children in the placebo arms. This corresponds to a risk difference of 18 fewer cases of intussusception with RotaTeq per 100,000 children with the 95% CI indicating from 26 fewer to 191 more per 100,000 (data not shown). Pooled results showed no increased risk of intussusception in children receiving RotaTeq when compared to placebo (RR 0.33, 95% CI 0.01 to 8.16; 7488 participants, 5 comparisons in 2 trials; Analysis 2.8).

2.2. Secondary outcomes

2.2.1. Rotavirus diarrhoea: of any severity

Nine trials provided data for the efficacy of RotaTeq to prevent rotavirus diarrhoea of any severity in children; see Analysis 2.9 for one-year follow-up and Analysis 2.11 for two-year follow-up. Six trials were performed in low-mortality countries (TEQ Block 2007-EU/USA; TEQ Clark 2003-USA; TEQ Clark 2004-USA; TEQ Iwata 2013-JPN; TEQ Vesikari 2006a-FIN; TEQ Vesikari 2006b-INT), one trial in a medium-mortality country (TEQ Mo 2017-CHN), and two trials split into four country-level comparisons in high-mortality countries (TEQ Armah 2010-GHA; TEQ Armah 2010-KEN; TEQ Armah 2010-MLI; TEQ Zaman 2010-AS). Data below are grouped accordingly.

Low-mortality countries

RotaTeq reduced the number of cases of rotavirus diarrhoea by 70% at both one-year (RR 0.30, 95% CI 0.25 to 0.37; 8644 participants, 5 trials; Analysis 2.9) and two years follow-up (RR 0.30, 95% CI 0.25 to 0.37; 5223 participants, 2 trials; Analysis 2.11).

Medium-mortality countries

RotaTeq reduced the number of cases of rotavirus diarrhoea by 69% at two years follow-up (RR 0.31, 95% CI 0.21 to 0.46; 3864 participants, 1 trial; Analysis 2.9).

High-mortality countries

RotaTeq reduced the number of cases of rotavirus diarrhoea by 48% at one year (RR 0.52, 95% CI 0.28 to 0.94; 4806 participants, 3 comparisons from 1 trial; Analysis 2.9) and by 39% at two years (RR 0.61, 95% CI 0.45 to 0.83; 6744 participants, 4 comparisons from 2 trials; Analysis 2.11). Pooled results had significant heterogeneity at one-year (I^2 = 67%; see Analysis 2.9) and at two-year (I^2 = 69%; see Analysis 2.11) follow-up.

2.2.2. All-cause diarrhoea: of any severity

One trial performed in high-mortality Kenya (TEQ Armah 2010-KEN) provided data for the efficacy of RotaTeq to prevent all-cause diarrhoea of any severity; see Analysis 2.12 for one-year and Analysis 2.13 for two-year follow-up.

High-mortality countries

There was little or no difference between RotaTeq and placebo for any severity all-cause diarrhoea at one-year (RR 0.82, 95% CI 0.61 to 1.11; 1059 participants, 1 trial; Analysis 2.12) or at two-year follow-up (RR 0.89, 95% CI 0.68 to 1.16; 1059 participants, 1 trial; Analysis 2.13).

All-cause hospitalization

Data on all-cause hospitalization were provided from one trial carried out in Botswana, Tanzania, Zambia, and Zimbabwe (high-mortality countries) (TEQ Levin 2017-AF).

There was little or no difference between RotaTeq and placebo for all-cause hospitalization at two-year follow-up (RR 1.21, 95% CI 0.42 to 3.49; 202 participants, 1 trial; Analysis 2.14).

2.2.3. Rotavirus diarrhoea: requiring hospitalization or medical attention

RotaTeq reduced hospitalizations due to rotavirus diarrhoea episodes by 96% at one year of follow-up (RR 0.04, 95% CI 0.02 to 0.10; 57,134 participants, 1 trial; Analysis 2.15).

RotaTeq reduced the number of children requiring medical attention at one year of follow-up by 93% compared to placebo (RR 0.07, 95% CI 0.04 to 0.12; 57,134 participants, 1 trial; Analysis 2.16).

Data for medical attention and hospitalization rates due to all-cause diarrhoea were not estimable.

2.2.4. Reactogenicity

The incidence of fever (Analysis 2.17), diarrhoea (Analysis 2.18), and vomiting (Analysis 2.19) were evaluated after the first dose, second

dose, and third dose, and at the end of the follow-up period. We found little or no differences between the RotaTeq and placebo groups for any of the reactogenicity outcomes and time points. We noted significant heterogeneity for the pooled post-first dose data on fever (I^2 = 61%).

2.2.5. Adverse events that require discontinuation of vaccination schedule

Ten trials reported the number of adverse events leading to discontinuation of the vaccination schedule, with little or no difference between RotaTeq and placebo (RR 0.84, 95% CI 0.46 to 1.56; 15,471 participants, 10 trials; Analysis 2.20).

2.3. Dropouts before the end of trial

Similar numbers of children taking RotaTeq and placebo dropped out from trials before they ended (RR 0.98, 95% CI 0.90 to 1.08; 85,855 participants, 13 trials; Analysis 2.21).

2.4. Subgroup analyses

2.4.1. Rotavirus serotype (G- or P-type)

Rotavirus diarrhoea: of any severity

Four trials reported on serotype specific rotavirus diarrhoea of any severity (Analysis 2.22). There were fewer cases of G1, G2, G9, and P8 rotavirus diarrhoea in the RotaTeq group compared to the placebo group. Results were inconclusive for G3 and G4-specific rotavirus diarrhoea due to few events leading to wide 95% CIs. The pooled data for type G3 showed statistical heterogeneity (I^2 = 50%).

Rotavirus diarrhoea: severe

Three trials reported on serotype-specific severe rotavirus diarrhoea (Analysis 2.23). There were fewer severe cases of G4, G8, G9, and P6 rotavirus diarrhoea in the RotaTeq groups. Results were inconclusive for G1, G2, G3, P4, and P8 rotavirus diarrhoea due to few events or inconsistent results between trials leading to wide 95% CIs. The pooled data for G1 (I^2 = 97%), G3 (I^2 = 64%) and P8 (I^2 = 87%) types showed statistical heterogeneity.

2.4.2. HIV-infected children

One trial (TEQ Armah 2010-AF) performed HIV tests for 89% of participants and reported outcomes for HIV-infected children (38/1158); another trial (TEQ Levin 2017-AF) included and reported outcomes for HIV-exposed but uninfected and HIV-infected children. We included only HIV-infected children from this study in this subgroup analysis (Analysis 2.24).

Rotavirus diarrhoea: severe (up to two years of follow-up)

One of 21 children in the vaccine arm, and 0/17 children in the placebo arm had severe rotavirus diarrhoea at two-year follow-up; the result was inconclusive due to imprecision from the very wide 95% CI around the risk ratio (RR 2.45, 95% CI 0.11 to 56.68, 1 trial).

All-cause diarrhoea: severe (up to two years of follow-up)

Five of 21 children in the vaccine arm, and 1/17 children in the placebo arm had severe all-cause diarrhoea at two-year follow-up; the result was inconclusive due to imprecision from the very wide 95% CI around the risk ratio (RR 4.05, 95% CI 0.52 to 31.43, 1 trial).

All-cause death

Nine of 58 children in the vaccine arm, and 6/56 children in the placebo arm died; the result was inconclusive due to imprecision from the very wide 95% CI around the risk ratio (RR 1.36, 95% CI 0.53 to 3.45, 2 trials).

Serious adverse events (1-14 days after any dose)

Ten of 58 children in the vaccine arm, and 6/55 children in the placebo arm had a serious adverse event; the result was inconclusive due to imprecision from the very wide 95% CI around the risk ratio (RR 1.53, 95% CI 0.59 to 3.97, 2 trials).

2.5 Sensitivity analysis

2.5.1 Primary outcomes with high heterogeneity according to allocation concealment

There were no primary outcomes with high heterogeneity (I^2 > 75%).

3. Rotasiil

3.1. Primary outcomes

Summary of findings of primary outcomes are presented in Summary of findings 7 (Rotasiil, high-mortality countries).

3.1.1. Rotavirus diarrhoea: severe

High-mortality countries

Two trials conducted in India and Niger provided data for the efficacy of Rotasiil to prevent severe rotavirus diarrhoea in children. Rotasiil reduced severe rotavirus diarrhoea cases by 48% at one year (RR 0.52, 95% CI 0.33 to 0.81; 11,008 participants; Analysis 3.1) and by 44% by two years (RR 0.56, 95% CI 0.42 to 0.74; 11,008 participants; Analysis 3.2). The pooled data at one year (I^2 = 77%) and at two years (I^2 = 62%) showed statistical heterogeneity.

3.1.2. All-cause diarrhoea: severe

High-mortality countries

Two trials conducted in India and Niger provided data for the efficacy of Rotasiil to prevent severe all-cause diarrhoea in children. The trials showed little or no difference in the number of severe cases of diarrhoea with Rotasiil compared to placebo at one-year (RR 0.92, 95% CI 0.84 to 1.01; 11,008 participants; Analysis 3.3) and at two years (RR 0.94, 95% CI 0.88 to 1.01; 11,008 participants; Analysis 3.4) follow-up.

3.1.3. All-cause death

High-mortality countries

Two trials conducted in India and Niger reported on all-cause death. There was little or no difference in all-cause death between Rotasiil and placebo (RR 1.14, 95% CI 0.82 to 1.59; 11,586 participants; Analysis 3.5). Seventy-four deaths occurred among 5791 participants in the Rotasiil arms and 65 deaths occurred among 5795 participants in the placebo arms. This corresponds to a risk difference of 157 more deaths with Rotasiil per 100,000 children with the 95% CI indicating from 202 fewer to 662 more per 100,000 (data not shown). We present details of causes of death for each trial in Appendix 7.

3.1.4. All serious adverse events

High-mortality countries

Serious adverse events were reported in three trials conducted in India and Niger. Pooled results showed no statistically significant difference in the number of serious adverse events in the Rotasiil group compared with the placebo group (RR 0.98, 95% CI 0.92 to 1.04; 11,646 participants, 3 trials; Analysis 3.6).

In addition, another two trials conducted in India reported narrative results on serious adverse events: SIIL Zade 2014-INDb reported that "Two SAEs (urinary tract infections and septicaemia) unrelated to study vaccines were reported and both recovered uneventfully", but it was not clear in which group the events took place. No SAEs were reported among 18 infants and 18 toddlers in SIIL Zade 2014-INDa, but the total number of participants per group were not reported.

3.1.5. Serious adverse events: intussusception

High-mortality countries

Two trials conducted in India and Niger reported on cases of intussusception. Seven cases of intussusception were reported in a total of 5791 children in the Rotasiil arms compared with seven cases of intussusception in 5795 children in the placebo arms. This corresponds to a risk difference of two fewer cases of intussusception with Rotasiil per 100,000 children with the 95% CI indicating from 79 fewer to 210 more per 100,000 (data not shown). Pooled results showed no increased risk of intussusception in children receiving Rotasiil when compared to placebo (RR 0.98, 95% CI 0.35 to 2.74; 11,586 participants; Analysis 3.7).

3.2. Secondary outcomes

3.2.1. Rotavirus diarrhoea: of any severity

Two trials provided data for the efficacy of Rotasiil to prevent rotavirus diarrhoea of any severity in children. Rotasiil reduced the number of cases of rotavirus diarrhoea of any severity by 33% at one-year (RR 0.67, 95% CI 0.59 to 0.76; 11,008 participants; Analysis 3.8) and by 23% at two-year follow-up (RR 0.77, 95% CI 0.71 to 0.84; 11,008 participants; Analysis 3.9).

3.2.2. Rotavirus diarrhoea: requiring hospitalization

Rotasiil reduced the number of children requiring hospitalization due to rotavirus diarrhoea by 41% at one-year (RR 0.59, 95% CI 0.39 to 0.88; 7500 participants, 1 trial) and at two years (RR 0.66, 95% CI 0.52 to 0.85, 7500 participants, 1 trial) follow-up compared to placebo (Analysis 3.10).

3.2.3. All-cause diarrhoea of any severity

There was little or no difference between Rotasiil and placebo for any severity all-cause diarrhoea at one-year (RR 0.97, 95% CI 0.90 to 1.04; 3508 participants, 1 trial; Analysis 3.11) and at two years follow-up (RR 0.96, 95% CI 0.90 to 1.02; 3508 participants, 1 trial; Analysis 3.12).

3.2.4. Reactogenicity

The incidence of fever (Analysis 3.13), diarrhoea (Analysis 3.14), and vomiting (Analysis 3.15) were evaluated after any dose in four trials. We found little or no difference between the Rotasiil and placebo groups for any of the reactogenicity outcomes.

3.2.5. Adverse events requiring discontinuation

One trial reported no adverse events leading to discontinuation of the vaccination schedule (RR not estimable, 7500 participants; Analysis 3.16).

3.2.6. Dropouts before the end of trial

Similar numbers of children taking Rotasiil or placebo dropped out from trials before they ended (RR 0.93, 95% CI 0.66 to 1.32; 11,591 participants, 2 trials; Analysis 3.17).

3.3. Subgroup analyses

3.3.1. Rotavirus serotype (G- or P-type)

Rotavirus diarrhoea: severe

Two trials (SIIL Isanaka 2017-NER; SIIL Kulkarni 2017-IND) reported on G- and P-type specific severe cases of rotavirus diarrhoea (Analysis 3.18).

There were fewer severe cases of rotavirus diarrhoea in the Rotasiil groups for G1, G2, Gp, P4, P6; results were inconclusive due to inconsistency in the results or few events leading to wide 95% CIs for G3, G4, G8, G12, and P8. The pooled data showed statistical heterogeneity for G1 (I^2 = 49%), G2 (I^2 = 47%), and G3-specific severe rotavirus diarrhoea (I^2 = 73%).

Rotavirus diarrhoea: any severity

One trial (SIIL Isanaka 2017-NER) reported on G- and P-type specific cases of rotavirus diarrhoea of any severity (Analysis 3.19).

There were fewer cases of rotavirus diarrhoea in the Rotasiil groups for G1, G2, P4, P6; results were inconclusive due to few events leading to wide 95% CIs for G3, G4, G8, G9, G12, and P8.

The included Rotasiil trials did not report separate data on immunocompromised or malnourished subgroups.

3.4 Sensitivity analyses

3.4.1 Primary outcomes with high heterogeneity according to allocation concealment

We rated all trials at low risk of bias for allocation concealment for the outcome where heterogeneity was high (I^2 > 75%); see Analysis 3.1 (I^2 = 77%).

4. Rotavac

4.1. Primary outcomes

Summary of findings of primary outcomes are presented in Summary of findings 8 (Rotavac, high-mortality countries).

4.1.1. Rotavirus diarrhoea: severe

High-mortality countries

One trial conducted in India provided data for the efficacy of Rotavac to prevent severe rotavirus diarrhoea in children. Rotavac reduced severe rotavirus diarrhoea cases by 57% at one year (RR 0.43, 95% CI 0.30 to 0.60; 6799 participants; Analysis 4.1), by 48% in the second year of life (RR 0.52, 95% CI 0.33 to 0.81; 6516 participants; Analysis 4.2), and by 54% by up to two years follow-up (RR 0.46, 95% CI 0.35 to 0.60; 6541 participants; Analysis 4.3).

4.1.2. All-cause diarrhoea: severe

High-mortality countries

One trial conducted in India provided data for the efficacy of Rotavac to prevent severe all-cause diarrhoea in children. The trial showed a reduction in the number of severe cases of diarrhoea with Rotavac compared to placebo at one year by 16% (RR 0.84, 95% CI 0.71 to 0.98; 6799 participants; Analysis 4.4).

4.1.3. All-cause death

High-mortality countries

Two trials conducted in India reported on all-cause death. There was little or no difference in all-cause death between Rotavac and placebo (RR 0.88, 95% CI 0.50 to 1.56; 8155 participants, Analysis 4.5). Thirty-five deaths occurred among 5549 participants in the Rotavac arms and 18 deaths occurred among 2606 participants in the placebo arms. This corresponds to a risk difference of 83 fewer deaths with Rotavac per 100,000 children with the 95% CI indicating from 345 fewer to 387 more per 100,000 (data not shown). We present details of causes of death for each trial in Appendix 7.

4.1.4. All serious adverse events

High-mortality countries

Serious adverse events were reported in three trials conducted in India. Pooled results showed no statistically significant difference in the number of serious adverse events in the Rotavac group compared with the placebo group (RR 0.93, 95% CI 0.85 to 1.02; 8210 participants, 3 trials; Analysis 4.6).

4.1.5. Serious adverse events: intussusception

High-mortality countries

Four trials conducted in India reported on cases of intussusception. Eight cases of intussusception were reported in a total of 5764 children in the Rotavac arm compared with three cases of intussusception in 2818 children in the placebo arm. This corresponds to a risk difference of 35 more cases of intussusception with Rotavac per 100,000 children with the 95% CI indicating from 69 fewer to 428 more per 100,000 (data not shown). Pooled results were inconclusive due to few events leading to wide 95% CIs (RR 1.33, 95% CI 0.35 to 5.02; 8582 participants; Analysis 4.7).

4.2. Secondary outcomes

4.2.1. Rotavirus diarrhoea: of any severity

One trial provided data for the efficacy of Rotavac to prevent rotavirus diarrhoea of any severity in children. Rotavac reduced the number of cases of rotavirus diarrhoea of any severity by 34% at both one-year (RR 0.66, 95% CI 0.56 to 0.78; 6799 participants, 1 trial; Analysis 4.8) and two-year follow-up (RR 0.66, 95% CI 0.57 to 0.76; 6541 participants, 1 trial; Analysis 4.2).

4.2.2. Rotavirus diarrhoea: requiring medical attention

Rotavac reduced the number of children requiring medical attention due to rotavirus diarrhoea at one year of follow-up by 31% compared to placebo (RR 0.69, 95% CI 0.58 to 0.81; 6799 participants, 1 trial; Analysis 4.11).

4.2.3. Reactogenicity

The incidence of fever (Analysis 4.12), diarrhoea (Analysis 4.13), and vomiting (Analysis 4.14) were evaluated after the first dose in two trials, second dose in one trial, and third dose in one trial. We found little or no difference between the Rotavac and placebo groups for most of the reactogenicity outcomes and time points, except for diarrhoea, which demonstrated an increase with Rotavac compared to placebo after the second dose (RR 1.55, 95% CI 1.00 to 2.41; 356 participants) and third dose (RR 4.09, 95% CI 2.11 to 7.92; 358 participants).

4.2.4. Dropouts before the end of trial

Similar numbers of children taking Rotavac or placebo dropped out from trials before they ended (RR 0.85, 95% CI 0.57 to 1.29; 8215 participants, 3 trials; Analysis 4.15).

4.3. Subgroup analyses

4.3.1. Rotavirus serotype (G- or P-type)

Rotavirus diarrhoea: severe

One trial reported severe cases of rotavirus diarrhoea by G and P type (VAC Bhandari 2014-IND).

At one-year follow-up (Analysis 4.16), there were significantly fewer severe episodes of rotavirus diarrhoea in the Rotavac groups for G2P[4] (RR 0.39, 95% CI 0.22 to 0.69; 6541 participants) and G12P[6] (RR 0.31, 95% CI 0.13 to 0.74; 6541 participants); results were not significantly different between Rotavac and placebo for G1P[8] (RR 0.66, 95% CI 0.36 to 1.20; 6541 participants) and G12P[8] (RR 0.30, 95% CI 0.07 to 1.26; 6541 participants).

At two-year follow-up (Analysis 4.17) there were significantly fewer severe episodes of rotavirus diarrhoea in the Rotavac groups for G1P[8] (RR 0.59, 95% CI 0.38 to 0.93; 6541 participants), G2P[4] (RR 0.37, 95% CI 0.23 to 0.62; 6541 participants), G12P[6] (RR 0.31, 95% CI 0.13 to 0.74; 6541 participants), and G12P[8] (RR 0.31, 95% CI 0.10 to 0.96; 6541 participants).

The included Rotavac trials did not report separate data on immunocompromised or malnourished subgroups.

4.4 Sensitivity analyses

4.4.1 Primary outcomes with high heterogeneity according to allocation concealment

There were no primary outcomes with high heterogeneity (I^2 > 75%).

5 Post hoc subgroup analysis: Intussusception combining all vaccines

The risk of intussusception with any rotavirus vaccine compared with placebo was 1 fewer case per 10,000 children (95% CI from 2 fewer to 1 more case per 10,000) with a RR of 0.87 (95% CI 0.61 to 1.25, 43 trials, 212,636 participants, Table 2). The risk difference was similar in all mortality settings.

DISCUSSION

Rotavirus vaccines have been under development since the 1980s and, to date, four vaccines have been prequalified by the WHO (Rotarix, RotaTeq, Rotasiil, and Rotavac). A further two rotavirus vaccines are licensed for use in individual countries (LLR in China

and Rotavin in Vietnam, see Appendix 8). RRV-TV (RotaShield) has not been used since 1999. The four vaccines currently in use and prequalified by the WHO (Rotarix, RotaTeq, Rotasiil, and Rotavac) are the focus of this review.

Summary of main results

We included 60 trials with a total of 228,233 participants, that evaluated Rotarix (36 trials), RotaTeq (15 trials), Rotasiil (5 trials), and Rotavac (4 trials). Our analysis stratified the primary outcomes by country under-five child mortality strata (high-mortality countries, medium-mortality countries, and low-mortality countries; UNICEF 2019).

The trials were not designed or powered to detect an effect on preventing death or on the occurrence of possible rare serious adverse events, such as intussusception.

1. Rotarix

Fourteen Rotarix trials were conducted in low-mortality countries; five in Asia, five in Europe, and four in North America. See Summary of findings 1 for main results. Briefly, in infants under one year, Rotarix vaccination prevented 93% of cases of severe rotavirus diarrhoea (high-certainty evidence) and 52% of cases of severe all-cause diarrhoea (moderate-certainty evidence). In children up to two years, 90% of cases of severe rotavirus diarrhoea (high-certainty evidence) and 51% of cases of severe all-cause diarrhoea (moderate-certainty evidence) were prevented with Rotarix. For serious adverse events, children receiving Rotarix had 11% fewer events than those receiving placebo (high-certainty evidence).

Ten Rotarix trials were conducted in medium-mortality countries; five in Latin America, four in Asia, and one in Europe. See Summary of findings 2 for main results. Briefly, in infants under one year, Rotarix prevented 79% of cases of severe rotavirus diarrhoea (high-certainty evidence) and 36% of cases of severe all-cause diarrhoea (high-certainty evidence). In children up to two years, 77% of cases of severe rotavirus diarrhoea (high-certainty evidence) and 26% of severe all-cause diarrhoea cases (low-certainty evidence) were prevented with Rotarix. For serious adverse events, children receiving Rotarix had 15% fewer events than those receiving placebo (high-certainty evidence).

Twelve Rotarix trials were conducted in high-mortality countries; seven in Asia, four in Africa, and one in Latin America. See Summary of findings 3 for main results. Briefly, in infants under one year, Rotarix prevented 58% of cases of severe rotavirus diarrhoea (high-certainty evidence) and 27% of cases of severe all-cause diarrhoea (high-certainty evidence). In children up to two years, 35% of cases of severe rotavirus diarrhoea (moderate-certainty evidence) and 17% of cases of severe all-cause diarrhoea (high-certainty evidence) were prevented with Rotarix. Rotarix had little or no effect on serious adverse events in this setting (high-certainty evidence).

An effect of Rotarix on all-cause mortality (low- to moderate-certainty evidence) or on intussusception (low-certainty evidence) has not been shown in any of the settings.

2. RotaTeq

Nine RotaTeq trials were conducted in low-mortality countries; three in North America, two in Asia, two in Europe, one in Europe and the USA, and one in North America, Europe, Asia, and Latin America. See Summary of findings 4 for main results. Briefly, RotaTeq vaccination prevented 97% of cases of severe rotavirus diarrhoea in infants under one year (high-certainty evidence) and 96% of cases in children up to two years (high-certainty evidence). We found no RotaTeq trials that reported on severe all-cause diarrhoea. RotaTeq had little or no effect on serious adverse events in this setting (high-certainty evidence).

Two RotaTeq trials were conducted in medium-mortality countries; both in Asia. In addition, a large multicentre trial that was conducted on several continents included centres in a few medium-mortality countries, but was analysed in the low-mortality stratum since most centres were in low-mortality countries (see TEQ Vesikari 2006b-INT). See Summary of findings 5 for main results. Briefly, no medium-mortality stratum RotaTeq trials reported on severe rotavirus diarrhoea or on severe all-cause diarrhoea in infants under one year. In children up to two years, RotaTeq prevented 79% of cases of severe rotavirus diarrhoea (low-certainty evidence). For serious adverse events, an effect of the vaccine has not been shown (very low-certainty evidence).

Three RotaTeq trials were conducted in high-mortality countries; two in Asia and one in Africa. See Summary of findings 6 for main results. Briefly, in infants under one year, RotaTeq prevented 57% of cases of severe rotavirus diarrhoea (high-certainty evidence) and 20% of cases of severe all-cause diarrhoea (moderate-certainty evidence). In children up to two years, RotaTeq prevented 44% of cases of severe rotavirus diarrhoea (high-certainty evidence) and 15% of cases of severe all-cause diarrhoea (high-certainty evidence). RotaTeq had little or no effect on serious adverse events in this setting (moderate-certainty evidence).

An effect of RotaTeq on all-cause mortality (very low- to moderate-certainty evidence) or on intussusception (very low- to low-certainty evidence) has not been shown in any of the settings.

3. Rotasiil

No Rotasiil trials have been carried out in low- or medium-mortality countries. Five Rotasiil trials were conducted in high-mortality countries; four in India and one in Niger. See Summary of findings 7 for main results. Briefly, in infants under one year, Rotasiil vaccination prevented 48% of cases of severe rotavirus diarrhoea (high-certainty evidence) and resulted in little to no difference in severe all-cause diarrhoea (high-certainty evidence). In children up to two years, Rotasiil vaccination prevented 44% of cases of severe rotavirus diarrhoea (high-certainty evidence), but resulted in little to no difference in severe all-cause diarrhoea (high-certainty evidence). Rotasiil had little or no effect on serious adverse events in this setting (high-certainty evidence). An effect of Rotasiil on all-cause mortality (moderate-certainty evidence) or on intussusception (low-certainty evidence) has not been shown.

4. Rotavac

No Rotavac trials have been carried out in low- or medium-mortality countries. All four Rotavac trials were conducted in India, a high-mortality country. See Summary of findings 8 for main results. Briefly, in infants under one year, Rotavac prevented 57% of cases of severe rotavirus diarrhoea (moderate-certainty evidence) and 16% of cases of severe all-cause diarrhoea (moderate-certainty evidence). In children up to two years, Rotavac prevented 54% of cases of severe rotavirus diarrhoea (moderate-certainty evidence). Rotavac had little or no effect on serious adverse events in this

setting (moderate-certainty evidence). An effect of Rotavac on all-cause mortality (very low-certainty evidence) or on intussusception (very low-certainty evidence) has not been shown.

Overall completeness and applicability of evidence

We carried out this systematic review using RCTs. All the included trials were placebo-controlled, except for two Rotarix trials that compared vaccine to no intervention (RIX Colgate 2016-BGD; RIX Zaman 2017-BGD). The trials provided only limited data for special groups of children, such as malnourished or immunocompromised children.

Efficacy by setting

Rotarix and RotaTeq were highly efficacious in reducing severe rotavirus diarrhoea in low-mortality countries; widespread roll-out of rotavirus vaccines has led to major reductions in rotavirus hospitalizations in such settings (Hungerford 2017; Jonesteller 2017). In contrast, trials of Rotarix, RotaTeq, Rotasiil and Rotavac in high-mortality countries in Africa and Asia demonstrated a relatively lower vaccine efficacy. However, because of the higher burden of rotavirus disease in such countries, the absolute number of events prevented by vaccination is greater than in low-mortality countries (RIX Madhi 2010-AF).

A recent meta-analysis of observational studies (Burnett 2020a) documented that effectiveness of rotavirus vaccination against severe rotavirus gastroenteritis in children age < 12 months was 86%, 77% and 63-66% in low-, medium- and high-mortality countries, respectively.

The global impact of rotavirus vaccination on rotavirus hospitalizations, all-cause diarrhoea hospitalizations, and diarrhoea mortality, has recently been reviewed across a range of child mortality strata (Burnett 2020b).

Efficacy by age

Results from RCTs of Rotarix and RotaTeq found higher vaccine efficacy against severe rotavirus diarrhoea in the first year compared to the cumulative efficacy for the first and second years. Vaccine efficacy was lower in the second year of life to a degree that varied by setting; the difference in efficacy between the first and second years was greater in high-mortality (Rotarix: 63% up to one year versus 54% up to two years; RotaTeq: 57% versus 41%) compared to low-mortality countries (Rotarix: 84% up to one year versus 82% up to two years; RotaTeq: 92% versus 82%). Trials with Rotavac and Rotasiil were not carried out in any low-mortality country.

Reduced vaccine efficacy in high-mortality countries in trials reporting two years of follow-up could be explained either by waning of vaccine-induced immunity, or some protection in the placebo group resulting from more frequent exposure to natural rotavirus infection (RIX Madhi 2010-AF). A modelling study in Malawi concluded that reduced protection could be predicted in the absence of waning immunity (Pitzer 2019). In real-world vaccine effectiveness studies among children age 12-23 months, effectiveness was 84-86%, 54% and 58% in low-, medium- and high-mortality countries, respectively (Burnett 2020a). Additional vaccine doses have been explored in an attempt to extend the duration of protection in settings with a high burden of disease (Cunliffe 2016), although the predicted impact of one such strategy, an additional vaccine dose at nine months of age in a high-mortality setting (Malawi) was modest (Pitzer 2019).

Efficacy by schedule

Children who were enrolled in trials performed in low-mortality countries received the vaccines according to the country's immunization schedule. Trials performed in high-mortality countries examined the efficacy of Rotarix when administered at 10 to 14 weeks of age, a later age than is recommended in the Expanded Programme on Immunization (EPI) schedule. However, the 6- and 10-week Rotarix schedule used in EPI programmes has now been extensively evaluated following vaccine roll-out in high-mortality countries in Africa, with effectiveness comparable to efficacy trial estimates (Burnett 2020b).

All-cause diarrhoea

The impact of rotavirus vaccination on severe all-cause diarrhoea from a public health perspective is important, as laboratories in low-income countries may not routinely test for rotavirus infection. The effect on all-cause diarrhoea is a function of the contribution of rotavirus to all diarrhoea; the efficacy of the vaccine against rotavirus; and potential nonspecific effects of vaccination on gut health. Surprisingly, few trials reported vaccine efficacy against all-cause diarrhoea. Vaccine efficacy against all-cause diarrhoea of any severity was lower, meaning that vaccination may not have such a noticeable impact on milder episodes of diarrhoea occurring in the community (Hungerford 2018).

Mortality data

The included trials were not individually powered to detect a mortality effect. This review did not detect a difference in the number of deaths for children receiving any of the vaccines or placebo. Two post-vaccine implementation national surveillance studies from Mexico and Brazil reported that the introduction of Rotarix into the national immunization programme was associated with a decline in the number of diarrhoea-related deaths (Do Carmo 2011; Richardson 2010) in comparison with historical controls. A study from rural Malawi showed that diarrhoea deaths reduced by a third following Rotarix introduction (Bar-Zeev 2018).

Safety data

There was no detectable difference in the number of cases of intussusception for children receiving vaccine or placebo. While both Rotarix and RotaTeq have been associated with a low risk of intussusception in post-marketing studies in Europe, Americas and Australia, the benefits of vaccination are considered to outweigh the risk of vaccine-associated intussusception (Yen 2016). However, the risk of intussusception after administration of Rotarix was not higher than the background risk of intussusception in seven lower-income sub-Saharan African countries (Tate 2018).

Subgroup analyses

Rotavirus G- and P-types

All four rotavirus vaccines demonstrated efficacy against most of the rotavirus G- and P-types that were assessed (G1, G2, G3, G4, G8, G9, G12, P4, P6, P8), although results were often inconsistent between different countries and were imprecise due to few events.

Immunocompromised children

One Rotarix trial and two RotaTeq trials reported on immunocompromised children exposed to, or infected with, HIV. No differences were identified for efficacy or safety, but studies were not sufficiently powered for these endpoints. It is recommended that all HIV-infected or HIV-exposed infants be vaccinated with oral rotavirus vaccine, unless severely immunocompromised (Calles 2010). While specific information on rotavirus vaccination in many immunodeficiency conditions is lacking, infants with known severe combined immunodeficiency should not receive live rotavirus vaccine (Pinto 2016; Vesikari 2015).

Children with malnutrition

One Rotarix trial (RIX Salinas 2005-LA) found that Rotarix was significantly superior to placebo in preventing rotavirus diarrhoea in a subgroup of malnourished children.

Quality of the evidence

The trials included in this updated review were placebo-controlled (53 trials) or compared vaccine to no intervention (RIX Colgate 2016-BGD; RIX Zaman 2017-BGD); were conducted in Latin America, North America, Europe, Asia, and Africa; and the largest included over 60,000 children (RIX Ruiz-Palac 06-LA/EU; TEQ Vesikari 2006b-INT); we identified the need for such trials in the original version of the review (Soares-Weiser 2004). However, most children were followed for safety outcomes only.

The certainty of the evidence for efficacy outcomes (rotavirus diarrhoea of any severity and severe, and all-cause diarrhoea of any severity and severe) was either high or moderate. This was because most trials were assessed as being at low risk of bias, especially more recent trials, and pooled samples were usually large enough to generate precise estimates. When we downgraded efficacy outcomes to moderate certainty, this was due to selective reporting bias (only half of the studies reporting on severe rotavirus diarrhoea reported on severe all-cause diarrhoea), imprecision (low number of events), risk of bias (unclear selection bias or risk of performance and detection bias), or indirectness (only one study carried out in one high-mortality country makes it difficult to generalize to any high-mortality country).

The certainty of the evidence for all-cause mortality was low because the trials were not powered to detect an effect on mortality, and results were consequently imprecise with wide 95% CIs.

The certainty of the evidence for all serious adverse events was mostly high but was downgraded to moderate for RotaTeq in high-mortality countries due to imprecise results, and for Rotavac due to indirectness (all trials were carried out in India). For the rare serious adverse event intussusception, evidence was of low certainty for Rotarix, RotaTeq and Rotasiil due to imprecision with very wide 95% CIs. For Rotavac, evidence on intussusception was of very low certainty, due to imprecision and indirectness, as previously described.

Potential biases in the review process

We stratified all analyses by under-five child mortality rates (UNICEF 2019) to highlight the previously noted differences in rotavirus vaccine efficacy across countries. However, the use of stratified analyses can introduce bias when interpreting the implications of the review. The strata used may not reflect the current mortality rate in some of the countries, or the mortality rate when the trials were conducted. Alternatively, analyses could be stratified by prevalence or burden of rotavirus disease across different countries; however, this will likely result in similar problems.

The use of broad strata (i.e. low, medium, high) based on infant mortality are also unlikely to show differences at the country level. However, the stratified analysis provides indirect efficacy and safety results to countries that are not represented within the included trials. The largest RotaTeq trial (TEQ Vesikari 2006b-INT) was carried out mostly in low-mortality countries (Belgium, Finland, Germany, Italy, Puerto Rico, Sweden, Taiwan, USA), but also in some medium-mortality countries (Costa Rica, Jamaica, Mexico) and in one high-mortality country (Guatemala). Disaggregated data, split by country, were not available for this trial. The data were placed in the low-mortality stratum and potentially resulted in under-representation in the medium-mortality stratum for RotaTeq.

Agreements and disagreements with other studies or reviews

We identified three systematic reviews of RCTs evaluating the efficacy or safety of rotavirus vaccines that have been conducted since the 2012 update of this Cochrane Review:

- Lamberti 2016 included RCTs and observational studies and evaluated region-specific effectiveness of Rotarix, RotaTeq and Rotavac. The systematic review found that rotavirus vaccination was both efficacious and effective in preventing rotavirus diarrhoea, severe rotavirus diarrhoea and rotavirus hospitalizations among children under five across all regions, with higher efficacy in more developed regions.
- Velázquez 2017 included RCTs and post-licensure observational studies from Latin America and the Caribbean, and found that Rotarix reduced the risk of any-severity rotavirus-related gastroenteritis by 65% and of severe gastroenteritis by 82% versus placebo. Both Rotarix and RotaTeq vaccines significantly reduced the risk of hospitalization and emergency visits by 85% for Rotarix and by 90% for RotaTeq. Vaccination with RotaTeq or Rotarix did not increase the risk of death, intussusception, or other severe adverse events.
- Buyse 2014 presented an integrated meta-analysis of safety and reactogenicity data of 28 Rotarix RCTs and found that Rotarix has a reactogenicity and safety profile similar to placebo.
- Clark 2019 conducted a meta-regression analysis of RCTs of rotavirus vaccines and demonstrated that efficacy fell more rapidly, to 44% by 12 months of age, in high-mortality settings.
- Skansberg 2021 summarized the available clinical trial and post-introduction evidence for the newer vaccines Rotasiil, Rotavac, and Rotavin, and concluded that all three vaccines had demonstrated safety and efficacy against rotavirus diarrhoea.
- Lu 2019 assessed the risk of intussusception in RCTs of Rotarix, RotaTeq, Rotasiil, Rotavac, and RV3-BB and found that the vaccines were not associated with an elevated risk of intussusception among neonates or infants.

The findings of these systematic reviews agree with the findings of our review, although the scope of these reviews was narrower; they reviewed efficacy or safety only, or were limited to a specific geographical region, or reviewed only one of the vaccines.

Consequently, we included more trials in our review. Finally, the major findings of this review update, including new evidence from five trials of Rotasiil, are not significantly different from the previous Soares-Weiser 2019 review.

Relationship to current policies

The data in this review support the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization's recommendation for "the inclusion of rotavirus vaccination of infants into all national immunization programmes" with a stronger recommendation for countries where "diarrhoeal deaths account for ≥ 10% of mortality among children aged < 5 years" (SAGE 2009; WHO 2020).

AUTHORS' CONCLUSIONS

Implications for practice

- Rotarix, RotaTeq, Rotasiil and Rotavac are efficacious vaccines in preventing rotavirus diarrhoea. Rotarix and RotaTeq have comparable safety and efficacy profiles and have been evaluated in different settings worldwide. The evidence on Rotasiil is currently limited to studies from India and Niger, and evidence on Rotavac to India only. The systematic review data support the global WHO rotavirus vaccine recommendation (SAGE 2009; SAGE 2012; WHO 2021b).
- The data from the included RCTs indicate that Rotarix, RotaTeq, Rotasiil, and Rotavac result in little to no difference in intussusception risk compared to a placebo or to no vaccine and, importantly, a lower risk of intussusception compared to the magnitude observed with the first licensed vaccine (RRV-TV, RotaShield). However, since the data cannot exclude a smaller risk of intussusception or other rare serious adverse events, routine vaccine introduction should be accompanied by safety surveillance (Buttery 2011; Groome 2020; Patel 2011; Reddy 2020; Shui 2012; Weintraub 2014).

Implications for research

Placebo-controlled efficacy trials of Rotarix and RotaTeq have been undertaken in representative populations of low-, medium-, and high-mortality countries and do not require repetition; efficacy or effectiveness trials of Rotavac and Rotasiil outside of India should be considered if these vaccines are introduced globally. Further research would be valuable in the following areas:

- Continued post-introduction studies to examine the impact and effectiveness of rotavirus vaccination, particularly in high-mortality countries.
- A greater understanding of the lower vaccine efficacy observed in high-mortality countries in Africa and Asia compared to low-mortality countries in the first and second years of life.
- Studies assessing the impact of malnutrition on rotavirus vaccine performance.
- Studies to assess the potential benefit of alternative dosage schedules of rotavirus vaccine, especially in high-mortality countries (e.g. neonatal dosing, additional dosing).
- Studies to assess risk and severity of rotavirus diarrhoea in older vaccinated children.
- Continued post-introduction studies in representative countries should examine vaccine safety with particular respect to intussusception and should analyse the risk/benefit of rotavirus vaccination (Patel 2011). Given the rarity of the event, data from different countries may need to be pooled (Escolano 2011; Escolano 2015), or self-controlled case series analyses may need to be carried out (Carlin 2013; Stowe 2016; Tate 2018; Yih 2014).

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RIX Salinas 2005-LA *{published data only}*

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RIX Steele 2008-ZAF *{published data only}*

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RIX Steele 2010a-ZAF *{published data only}*

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RIX Steele 2010b-ZAF *{published data only}*

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RIX Tregnaghi 2011-LA *{published data only}*

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RIX Vesikari 2004b-FIN *{published data only}*

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RIX Vesikari 2011-FIN *{published data only}*

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RIX Ward 2006-USA *{published data only}*

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RIX Zaman 2009-BGD *{published data only}*

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

RIX Anh 2011-PHL

Study characteristics	
Methods	RCT **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. 2 doses of RIX4414* plus 1 dose of placebo according to a PL-V-V schedule 2. 2 doses of RIX4414* plus 1 dose of placebo according to a V-PL-V schedule 3. 3 placebo doses * Human rotavirus (Rotarix) 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
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity, including fever, diarrhoea and vomiting, 8 days after each dose (collected from GSK report) 2. Adverse events leading to discontinuation 3. Serious adverse events 4. Fatal serious adverse events 5. Dropouts 6. * Rotavirus diarrhoea, rotavirus antigen isolated from any of the stool samples collected from children with diarrhoea episodes, up to 1 month after last dose 7. * All-cause diarrhoea, up to 1 month after last dose **Outcomes to measure immunogenicity** 8. Anti-rotavirus IgA antibody seroconversion, ≥ 20 U/mL * Outcome reported as proportion (P) with 95% CI. Events (n) and totals (N) were estimated by using the values when 2 formulae for the standard error (SE) converged.

RIX Anh 2011-PHL *(Continued)*

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) High-mortality country
Notes	Study known as *RV1 GSK[063] 2008-AS* in previously published versions of this review **Date:** March to September 2007 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "This study will provide data on the immune response and safety of GSK Biologicals' HRV [human rotavirus] liquid vaccine when given along with the routine infant immunizations in Philippines." "The study also[...]explored the potential effect of scheduling of the HRV [human rotavirus] vaccine doses with respect to the existing routine vaccination schedules".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated Quote: "Block randomization scheme (2:2:1 ratio) with standard SAS program was used".
Allocation concealment (selection bias)	Low risk	Central allocation Quote: "Based on the block size, the vaccine doses were distributed to each of the study centers".
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel were blinded. Quote: "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". Quote: "The placebo was identical to the vaccine in composition".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across groups with reasons for dropout/exclusion reported
Selective reporting (reporting bias)	Low risk	All prepublished outcomes included
Other bias	Low risk	No apparent other bias

RIX Anh 2011-VNM

Study characteristics

Methods	RCT **Length of follow-up:** 1 month after last dose **Adverse event data collection methods:** not reported

RIX Anh 2011-VNM *(Continued)*

Participants	**Number:** 375 enrolled; ATP safety cohort: 352; ATP immunogenicity cohort: 330 **Inclusion criteria:** healthy infants aged 6 to 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. 2 doses of RIX4414* plus 1 dose of placebo according to a V-V-PL schedule 2. 2 doses of RIX4414* plus 1 dose of placebo according to a V-PL-V schedule 3. 3 placebo doses * Human rotavirus [Rotarix] 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
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity, including fever, diarrhoea and vomiting, 8 days after each dose (collected from GSK report) 2. Adverse events leading to discontinuation 3. Serious adverse events 4. Fatal serious adverse events 5. Dropouts 6. * Rotavirus diarrhoea, rotavirus antigen isolated from any of the stool samples collected from children with diarrhoea episodes, up to 1 month after last dose (outcome not included in the prepublished protocol) 7. * All-cause diarrhoea, up to 1 month after last dose (outcome not included in the prepublished protocol) **Outcomes to measure immunogenicity** 8. Anti-rotavirus IgA antibody seroconversion, ≥ 20 U/mL * Outcome reported as proportion (P) with 95% CI. Events (n) and totals (N) were estimated by using the values when 2 formulae for the standard error (SE) converged.
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 centres) High-mortality country
Notes	Study known as *RV1 GSK[051] 2008-AS* in previously published versions of this review **Date:** September 2006 to March 2007 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "To provide specific data on immunogenicity of GSK Biologicals' human rotavirus liquid vaccine, when co-administered with the routine Expanded Program of Immunization (EPI) in Viet-

RIX Anh 2011-VNM *(Continued)*

	nam. The study will also assess reactogenicity and safety of the human rotavirus liquid vaccine relative to the placebo".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated Quote: "Block randomization scheme (2:2:1 ratio) with standard SAS program was used".
Allocation concealment (selection bias)	Low risk	Central allocation Quote: "Based on the block size, the vaccine doses were distributed to each of the study centers".
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel were blinded. Quote: "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". Quote: "The placebo was identical to the vaccine in composition".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across groups with reasons for dropout/exclusion reported
Selective reporting (reporting bias)	Unclear risk	One outcome (rotavirus diarrhoea) not included in the prepublished protocol
Other bias	Low risk	No apparent other bias

RIX Bernstein 1998-USA

Study characteristics

Methods	RCT **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	1. RIX4414 (Rotarix): 10^5 PFU; 21 participants 2. Placebo: 20 participants **Schedule:** 2 doses given 6 to 10 weeks apart
Outcomes	**Clinical outcome measures** 1. Reactogenicity: diarrhoea defined as > 3 stools that were looser than normal in a 24-hour period; fever defined as a temperature > 100.4 °F obtained rectally in infants

RIX Bernstein 1998-USA *(Continued)*

	2. Serious adverse events 3. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 4. Vaccine virus shedding: rotavirus shedding after immunization; combined time points (review included data from combined time points) 5. Seroconversion: ≥ 4-fold rise in rotavirus IgA antibody (serum and stool) (review included data from after dose 1 and dose 2)
Immunization status	Rotavirus vaccine was separated from all other infant vaccines by at least 2 weeks.
Location	Cincinnati, USA Low-mortality country
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

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) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Trial report did not provide enough details.

RIX Bernstein 1999-USA

Study characteristics

Methods	RCT **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,

RIX Bernstein 1999-USA *(Continued)*

	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 (Rotarix) 1. 89-12 (a precursor of RIX4414 (Rotarix)): 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".
Outcomes	**Clinical outcome measures** 1. All-cause diarrhoea: gastroenteritis defined as vomiting (> 1 hour after feeding), diarrhoea (≥ 3 looser than normal stools in a 24-hour period), or both; measured up to 2 years 2. Severe rotavirus diarrhoea: severity assessed using a scoring system with a "20-point scale identical to that used in previous rotavirus trials. In this system, points are assigned according to the duration and severity of diarrhoea and vomiting, the severity of fever, and the presence of dehydration or hospital admissions for each episode of gastroenteritis. A score greater than 8 was prospectively defined as severe, and a score more than 14 as very severe"; measured up to 2 years 3. Rotavirus diarrhoea: "An illness was classified as caused by rotavirus if a stool specimen collected no later than 7 days after resolution of symptoms contained rotavirus antigen. All episodes of rotavirus gastroenteritis occurring between the second vaccination and the end of the study were included"; measured up to 7 days 4. Reactogenicity: "Parents filled out a diary card for 7 days after each dose. Signs included were: daily (evening) rectal temperatures, diarrhoea, vomiting, and the number and consistency of all stools"; measured up to 7 days 5. All-cause death; measured up to 2 years 6. Emergency department visit; measured up to 2 years 7. Rotavirus diarrhoea requiring hospitalization **Outcomes to measure immunogenicity** 8. Vaccine virus shedding (review included after dose 2 data) 9. Immunogenicity (ELISA): "Serum samples were analysed for IgA and IgG antibody to rotavirus by an ELISA" and "neutralising antibody to the 89-12 strains by an antigen reduction assay" (only rotavirus-specific IgA results reported in this review from after dose 2 time point)
Immunization status	Other vaccines separated from the trial vaccines by at least 2 weeks
Location	Cincinnati, Baltimore, and Sellersville, USA Low-mortality country

RIX Bernstein 1999-USA *(Continued)*

Notes	**Date:** August 1997 to June 1998 **Source of funding:** Virus Research Institute, Inc. (now Avant Immunotherapeutics Inc.)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Infants were assigned to receive either 89-12 or placebo according to a computer-generated randomization 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) All outcomes	Unclear risk	Double-blind, no details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No impact on intervention effect estimate Quote: "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

RIX Colgate 2016-BGD

Study characteristics

Methods	RCT, open-label non-placebo controlled trial **Length of follow-up:** outcomes measured at 1 year **Adverse event data collection methods:** Passive**:** All adverse events following interventions were captured for 48 hours following each intervention and were scored for probable, possible, or unlikely relationship to each intervention. All missing protocol-defined events were captured as protocol deviations and reported annually. Comprehensive safety reports were submitted semi-annually to the study's Independent Medical Monitor and to the Data and Safety Monitoring Board.
Participants	**Number:** 700 enrolled; 593 evaluable **Age range:** birth to age 7 days at enrolment, 10-17 weeks at vaccine administration **Inclusion criteria:** Healthy infant aged 0 to 7 days, no obvious congenital abnormalities or birth defects, no abnormal (frequency and consistency) stools since birth, stable household with no plans to leave the area for the next one year

RIX Colgate 2016-BGD *(Continued)*

	Exclusion criteria: Parents are not willing to have child vaccinated at the field clinic or to have child's blood drawn, parents are planning to enrol child into another clinical study, mother not willing to have blood drawn and breast milk extracted, parents not willing to have field research assistant in home twice a week, history of seizures or other apparent neurologic disorders, infant received any vaccines before start of study, except Bacillus Calmette-Guerin (BCG), infant has any sibling currently or previously enrolled in this study (including a twin)
Interventions	1. Rotarix dose 1 at 10 weeks, dose 2 at 17 weeks (350 enrolled participants) 2. No Rotarix vaccine (350 enrolled participants)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea (severe) 2. All-cause diarrhoea (severe) 3. All-cause deaths 4. Rotavirus diarrhoea (any severity) 5. All-cause diarrhoea (any severity) 6. Dropouts from the trial
Immunization status	Along with Rotarix at 10 and 17 weeks of age, the polio vaccine intervention was the administration of an injected, inactivated polio vaccine (IPV) dose replacing the fourth dose of tOPV at 39 weeks of age. In addition to the vaccine interventions, study children received all standard EPI vaccines through the study clinic.The national Bangladesh Expanded Program on Immunizations (EPI) schedule includes BCG at birth; pentavalent vaccine (DPT, HPV, Hib) at 6, 10, and 14 weeks; bivalent measles-rubella at 40 weeks; and monovalent measles at 65 weeks
Location	Single site, Bangladesh High-mortality country
Notes	**Date:** May 2011 to November 2013 **Source of funding:** Bill and Melinda Gates Foundation **Study rationale:** The primary objective was to determine the efficacy of a 2-dose Rotarix oral rotavirus vaccine (given at 10 and 17 weeks of age) to prevent rotavirus diarrhoea in the first year of life.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized using permuted blocks with random block size selection
Allocation concealment (selection bias)	Low risk	All clinical investigators and laboratories were masked to vaccine arm, but medical officers were not.
Blinding (performance bias and detection bias) All outcomes	High risk	Rotarix versus no intervention, unable to blind (no placebo)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary ITT analysis, moderate attrition

RIX Colgate 2016-BGD *(Continued)*

Selective reporting (reporting bias)	Low risk	All relevant outcomes appeared to be reported, protocol published
Other bias	Low risk	No other bias apparent

RIX Dennehy 2005-NA

Study characteristics	
Methods	RCT **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	1. RIX4414 (Rotarix) 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
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: fever, irritability/fussiness, diarrhoea, vomiting, loss of appetite and cough/runny nose; measured during 15 days post-vaccination 2. Serious adverse events 3. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 4. Viral shedding: viral shedding in any stool specimen collected between first dose and 2 months after second vaccine dose (review included after dose 2 data) 5. Seroconversion: anti-rotavirus IgA ELISA ≥ 20 units/mL in participants negative for rotavirus antibody before the first dose of vaccine (review included data from 2 months after dose 2)

RIX Dennehy 2005-NA *(Continued)*

Immunization status	Vaccine or placebo given concomitantly with diphtheria-tetanus-acellular pertussis, inactivated poliovirus, *H. 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 Low-mortality countries
Notes	**Date:** 13 December 2000 to 2 August 2002 **Source of funding:** GlaxoSmithKline Biologicals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS programme
Allocation concealment (selection bias)	Low risk	Central allocation Quote: "double blind randomized unbalanced allocation scheme (2:2:1 ratio)"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel; Quote: "Study personnel and families were blinded to group assignment until study completion".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups Quote: "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

RIX GSK[021] 2007-PAN

Study characteristics

Methods	RCT **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

RIX GSK[021] 2007-PAN *(Continued)*

	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	1. RIX4414 (Rotarix): $10^{6.5}$ PFU*; 177 participants (randomized) 1.1 Received modified vaccine formulation 1.2 Received a licensed Rotarix vaccine *Dose unclear; in the same study, some used $10^{6.5}$ 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 Rotarix vaccine **Schedule:** 3 doses at 2, 4, and 6 months of age
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 8-day (days 0 to 7) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 31 days (days 0 to 30) after each dose, according to MedDRA classification; measured up to 31 days after vaccine/placebo 2. Serious adverse events: occurrence throughout entire study period; measured up to 31 days after vaccine/placebo 3. Dropouts: measured up to 31 days after vaccine/placebo 4. All-cause death 5. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 6. Viral shedding: number (%) of participants with rotavirus in at least 1 stool (review included data from combined time points) 7. Seroconversion: appearance of anti-rotavirus antibody concentration ≥ 20 U/mL in participants negative for rotavirus before vaccination (review included data from 2 months after dose 1 and 2 months after dose 2, and 1 month after dose 3)
Immunization status	Use of other vaccines not mentioned
Location	1 centre in Panama Medium-mortality country
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 human rotavirus [Rotarix] vaccine"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS programme

RIX GSK[021] 2007-PAN *(Continued)*

Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Parent/guardian and study personnel were not aware of the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	Low risk	203/228 participants completed the study. Reasons for withdrawal were reported and balanced between groups.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Unclear risk	No details

RIX GSK[033] 2007-LA

Study characteristics	
Methods	RCT **Length of follow-up:** 1 month after dose 2 **Adverse event data collection methods:** not reported
Participants	**Number:** 854 enrolled; 795 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	1. RIX4414 (Rotarix): $10^{6.5}$ PFU*; 730 participants (randomized) 1.1. Received vaccine Lot A 1.2. Received vaccine Lot B 1.3. Received vaccine Lot C *Dose unclear, some used $10^{6.5}$ 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 corresponded to months 0, 2, and 4 in the schedule
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 8-day (days 0 to 7) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 31 days (days 0 to 30) after each dose, according to MedDRA classification; measured up to 31 days after vaccine/placebo 2. Serious adverse events: occurrence throughout entire study period; measured up to 31 days after vaccine/placebo

RIX GSK[033] 2007-LA *(Continued)*

	3. Dropouts: measured up to 31 days after vaccine/placebo 4. All-cause death 5. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 6. Vaccine virus shedding: presence of rotavirus antigen in stool samples collected on day of vaccination and on planned days following each dose in a subset of participants [review included data from combined time points] 7. Seroconversion: appearance of serum anti-rotavirus IgA antibody concentrations ≥ 20 U/mL [review included data from 2 months after dose 2]
Immunization status	Use of other vaccines not mentioned
Location	7 study centres (2 in Colombia, 1 in Mexico, and 4 in Peru) Medium-mortality countries
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 vaccine in terms of immunogenicity and safety when given to healthy infants at 2 and 4 months of age"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS programme
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Parent/guardian and study personnel were not aware of the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	Low risk	795/854 completed the study. Reasons for dropping out were reported and were balanced between study groups.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Unclear risk	No details

RIX GSK[041] 2007-KOR

Study characteristics

Methods	RCT **Length of follow-up:** 2 months after dose 2

RIX GSK[041] 2007-KOR *(Continued)*

	Adverse event data collection methods: not reported
Participants	**Number:** 155 enrolled; 151 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	1. RIX4414 (Rotarix): $10^{6.5}$ 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
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 15-day (days 0 to 14) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 43 days (days 0 to 42) after each dose, according to MedDRA classification; up to 43 days after vaccine/placebo 2. Serious adverse events: no definition; occurrence throughout the entire study period (up to 2 months after dose 2) 3. Dropouts: measured up to 2 months after dose 2 4. Rotavirus diarrhoea: presence of rotavirus in gastroenteritis episode stools collected from dose 1 of vaccine/placebo up to 2 months after dose 2 5. All-cause death 6. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 7. Seroconversion: appearance of anti-rotavirus immunoglobulin A antibody concentration 20 U/mL in participants who were seronegative before vaccination (review included data from 2 months after dose 2)
Immunization status	*H. influenzae* type b vaccine administered concomitantly along with the 2 doses of vaccine/placebo and at 2 months after dose 2; other routine childhood vaccines were to be given at least 14 days before trial vaccine/placebo
Location	6 centres in Korea Low-mortality country
Notes	**Date:** 15 July 2005 to 11 May 2006 **Registration number:** NCT00134732 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to assess immunogenicity and safety of 2 doses of the HRV [human rotavirus] vaccine in Korean infants aged approximately 2 months at the time of the first dose"

Risk of bias

Bias	Authors' judgement	Support for judgement

RIX GSK[041] 2007-KOR *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS programme
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Parent/guardian and study personnel were not aware of the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/103 participants in the vaccine arm did not complete the study.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Unclear risk	No details

RIX GSK[101555] 2008-PHL

Study characteristics	
Methods	RCT **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	1. RIX4414 (Rotarix): $10^{6.5}$; 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 starting at 6–12 weeks of age according to a 0, 2-month schedule **Data from the lyophilized formulation, which is not yet approved or marketed, were not reported in review.*
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 15-day (day 0 to 14) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 31 (day 0 to 30) days after any doses of Rotarix vaccine or placebo, according to MedDRA classification

RIX GSK[101555] 2008-PHL *(Continued)*

	2. Serious adverse events: occurrence throughout entire study period (up to 31 days after final dose of vaccine/placebo) 3. Dropouts: measured up to 31 days after final dose of vaccine/placebo 4. Rotavirus diarrhoea: presence of rotavirus in gastroenteritis stools collected until 1 month after dose 2 5. All-cause death 6. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 7. Vaccine viral shedding in stool (review included data from combined time points) 8. Seroconversion: appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/mL in participants initially (i.e. before first dose of vaccine/placebo) negative for rotavirus (review included data from 2 months after dose 1, 1 month after dose 2, and combined dose 1 and 2 at 1 month after dose 2)
Immunization status	Use of other vaccines not mentioned
Location	1 study centre in the Philippines High-mortality country
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 [human rotavirus] vaccine given as a two-dose primary vaccination in healthy infants previously uninfected with HRV"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "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) All outcomes	Unclear risk	No details; Quote: "Double-blind with respect to each HRV [Rotarix] vaccine formulation and its respective placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/100 participants withdrawn from the vaccine group
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Unclear risk	No details

RIX Kawamura 2011-JPN

Study characteristics	
Methods	RCT **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 human rotavirus 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 rotavirus gastroenteritis
Interventions	1. Rotarix, 508 participants 2. Placebo, 257 participants **Schedule:** 2 doses according to a 0-, 1-month schedule
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Any rotavirus gastroenteritis leading to medical intervention and caused by the circulating wild-type rotavirus strains, from 2 weeks after dose 2 up to 2 years of age, stool sample collected as soon as possible but preferably not later than 7 days after the start of the episode 2. Severe rotavirus gastroenteritis (≥ 11 on the Vesikari scale) leading to a medical intervention and caused by the circulating wild-type rotavirus strains (a) of G1 type, (b) of non-G1 types, from 2 weeks after dose 2 up to 2 years of age 3. Each type of solicited symptom (including: cough, diarrhoea, fever, irritability, loss of appetite and vomiting) during the 8-day follow-up period after each dose 4. Adverse events leading to discontinuation of the trial 5. Serious adverse events, including intussusception, up to 2 years of age 6. Fatal serious adverse events 7. Dropouts before the end of the trial **Outcomes to measure immunogenicity** 8. Seroconversion in terms of anti-rotavirus IgA antibody, from 2 months after dose 2. Seroconversion was defined as the appearance of anti-rotavirus immunoglobulin A antibody concentration over 20 units (u)/mL) in infants initially (i.e. prior to the first dose of Rotarix) seronegative
Immunization status	Combined diphtheria and tetanus toxoids and acellular pertussis (DTPa) and hepatitis B (HBV) vaccines were allowed to be co-administered along with Rotarix vaccine/placebo
Location	Japan Low-mortality country
Notes	**Date:** June 2007 to November 2009 **Source of funding:** GlaxoSmithKline

RIX Kawamura 2011-JPN *(Continued)*

Registration number: NCT00480324

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS programme
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Parent/guardian and study personnel were not aware of the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusions balanced between groups
Selective reporting (reporting bias)	Low risk	Protocol published a priori, all prepublished outcomes reported
Other bias	Low risk	No apparent other bias

RIX Kerdpanich 2010-THA

Study characteristics

Methods	RCT **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 to 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 7 days, n = 50 4. Placebo reconstituted in buffer, n = 26 5. Placebo reconstituted in water, n = 26 * Lyophilized formulation containing at least $10^{6.0}$ $CCID_{50}$ of the RIX4414 strain

RIX Kerdpanich 2010-THA *(Continued)*

	Schedule: 2 doses at month 0 and 2
Outcomes	**Clinical outcome measures** 1. * Rotavirus diarrhoea, stool sample collected during diarrhoea episode, up to 2 months post-dose 2 2. * All-cause diarrhoea, up to 2 months post-dose 2 3. Reactogenicity, including fever, vomiting and diarrhoea, 15-day follow-up period after each dose (collected from GSK report) 4. Serious adverse events, up to 2 months post-dose 2 5. Fatal serious adverse events 6. Adverse events resulting in discontinuation (collected from GSK report) 7. Dropouts: measured up to 2 months after dose 2 (collected from GSK report) **Outcomes to measure immunogenicity** 8. Seroconversion, anti-rotavirus IgA antibody levels (cut off: ≥ 20 U/mL by ELISA), 2 months post-dose 2 9. Rotavirus antigen shedding in stool (review included data from combined time points) (collected from GSK report) * Outcome reported as proportion (P) with 95% CI. Events (n) and totals (N) were estimated by using the values when 2 formulae for the standard error (SE) converged.
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	2 centres in Thailand Medium-mortality country
Notes	Study known as *RV1 GSK[039] 2007-AS,* in previously published versions of this review **Date:** March to 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS programme
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Partially blind study. Quote: "Single blind"; not reported whether personnel or participants were blinded

RIX Kerdpanich 2010-THA *(Continued)*

		Quote: "The placebo was identical in appearance and composition to the active vaccine".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across groups with reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No apparent other bias

RIX Kim 2012-KOR

Study characteristics	
Methods	RCT **Length of follow-up:** 1 month post-dose 2 **Adverse event data collection methods:** Passive: Adverse events were recorded during the 8-day and 31-day follow-up period after each dose of RIX4414/placebo, respectively. SAEs were recorded during the entire study period
Participants	**Number:** 684 enrolled; 642 evaluable **Age range:** 6 to 12 weeks **Inclusion criteria:** Infants who the investigator believes that their parents/guardians can and will comply with the requirements of the protocol should be enrolled in the study: male or female between, and including, 6 to 12 weeks of age at the time of the first dose of the vaccination, healthy infants as established by medical history and clinical examination, born after a normal gestation period of between 37 and 41 weeks + 6 days inclusive, available vaccination history from vaccination diary cards or medical charts **Exclusion criteria:** Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the dose of study vaccine, or planned use during the study period, chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth, planned administration of a vaccine not foreseen by the study protocol within 30 days of the first dose of vaccine, with the exception of the routine infant vaccines, concurrently participating in another clinical study, confirmed or suspected immunosuppressive or immunodeficient condition, 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, history of allergic disease or reactions likely to be exacerbated by any component of the vaccine, acute disease at the time of enrolment, administration of immunoglobulins or any blood products, or both, since birth or planned administration during the study period, gastroenteritis (GE) within 7 days preceding the study vaccine administration, previous confirmed occurrence of RV GE, previous vaccination with rotavirus vaccine or planned use during the study period
Interventions	1. Rotarix 2. Placebo **Schedule:** 2 oral doses according to a 0-, 1-, or 2-month schedule
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause deaths

RIX Kim 2012-KOR *(Continued)*

	2. All serious adverse events 3. Serious adverse events: intussusception 4. Rotavirus diarrhoea: of any severity (up to 2 months follow-up) 5. All-cause diarrhoea: of any severity (up to 2 months follow-up) 6. Reactogenicity: vomiting, diarrhoea, fever 7. Adverse events requiring discontinuation 8. Dropouts from the trial **Outcomes to measure immunogenicity** 9. Seroconversion
Immunization status	Routine childhood vaccines as recommended by the local vaccination schedule were allowed to be administered concomitantly with RIX4414/placebo. These vaccines included the combined diphtheria-tetanus-acellular pertussis vaccine, *Haemophilus influenzae* type b vaccine, inactivated poliovirus vaccine and pneumococcal vaccine. The infants had received the BCG vaccine and 2 doses of hepatitis B vaccine prior to study enrolment.
Location	19 sites, Republic of Korea Low-mortality country
Notes	**Date:** August 2009 to July 2010 **Source of funding:** GlaxoSmithKline **Study rationale:** To evaluate immunogenicity, reactogenicity and safety of Rotarix™ vaccine in Korean Infants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All infants receiving RIX4414 or placebo were allocated into their respective groups using an internet based randomization tool SBIR (Internet based randomization system) according to 3:1 ratio". Quote: "A standard SAS® program generated a randomization list used to number the vaccines. A randomized (3:1) blocking scheme maintained the balance between the two treatments where a unique treatment number identified the study vaccine to be administered to the infants".
Allocation concealment (selection bias)	Low risk	The person in charge of the vaccination accessed the randomization system on the Internet. Upon providing a participant number and the age (6 - 12 weeks) for the infant, the randomization system used the minimization algorithm to determine the treatment number to be used for the participant. The actual treatment number used for first vaccination of the participant was recorded by the investigator in the eCRF (randomisation/treatment allocation section)
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Each dose of RIX4414 or placebo was administered in a blinded manner where the parents/guardians and the physicians were unaware of the vaccine administered".
Incomplete outcome data (attrition bias)	Unclear risk	462/684 completed the study; reasons for attrition provided

RIX Kim 2012-KOR *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	No indication of selective reporting bias
Other bias	Low risk	No apparent other bias

RIX Li 2013a-CHN

Study characteristics	
Methods	RCT **Length of follow-up:** 1 month **Adverse event data collection methods:** Passive: diary cards were provided to participants or their parents/guardians to record solicited adverse events for 8 days after each vaccination (day 0–7). Serious adverse events were recorded for the duration of the study.
Participants	**Number:** 50 enrolled; 50 evaluable **Age range:** 2 to 6 years old **Inclusion criteria:** participants were required to be of Chinese origin, in good health and free of obvious health problems.
Interventions	1. single dose of GlaxoSmithKline (GSK) Biologicals' human rotavirus (HRV) vaccine (444563). Each 1.5 mL dose of the liquid human RV vaccine contained at least ($CCID_{50}$) of the live attenuated RIX4414 human RV strain. 2. single-dose placebo
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events
Immunization status	Children were allowed to receive routine childhood vaccinations according to local immunization practice during the study period, with a minimum interval of at least 7 days between the administration of routine vaccines and the study vaccine or placebo.
Location	Single site, China Medium-mortality country
Notes	**Date:** March 2010 to April 2010 **Source of funding:** GlaxoSmithKline **Study rationale:** To assess the safety of a single oral dose of HRV vaccine when compared to placebo group, in terms of solicited adverse events (AEs) in healthy children aged 2 to 6 years

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Treatment allocation at the investigator site was performed using an internet-based randomization system (SBIR).

RIX Li 2013a-CHN *(Continued)*

Allocation concealment (selection bias)	Low risk	Treatment allocation at the investigator site was performed using an internet-based randomization system (SBIR).
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was conducted in a double-blind manner with respect to HRV vaccine and placebo. The parents/LARs of the infants, the study personnel and the investigator were unaware of the study vaccine administered (liquid HRV vaccine or placebo). The laboratory in charge of the laboratory testing was blinded to the treatment, and codes were used to link the participant and study (without any link to the treatment attributed to the participant) to each sample.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	Planned outcomes fully reported
Other bias	Low risk	No apparent other bias

RIX Li 2013b-CHN

Study characteristics	
Methods	RCT **Length of follow-up:** 1 month after second dose **Adverse event data collection methods:** Passive: diary cards were provided to participants or their parents/guardians to record solicited adverse events for 8 days after each vaccination (day 0–7). Serious adverse events were recorded for the duration of the study.
Participants	**Number:** 50 enrolled; 50 evaluable **Age range:** 6 to 16 weeks **Inclusion criteria:** Infants were required to be aged 6–16 weeks at the time of first vaccination. Participants were required to be of Chinese origin, in good health and free of obvious health problems.
Interventions	1. Rotarix: each 1.5 mL dose of the liquid HRV vaccine contained at least 106.0 median cell culture infective dose ($CCID_{50}$) of the live attenuated RIX4414 human RV strain. 2. Placebo **Schedule:** 2 oral doses according to a 0-, 1-month schedule
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause deaths 2. Serious adverse events 3. Intussusception 4. Reactogenicity: fever, diarrhoea, vomiting 5. Dropouts before the end of the trial 6. Adverse event requiring discontinuation

RIX Li 2013b-CHN *(Continued)*

	Outcomes to measure immunogenicity 7. Vaccine shedding 8. Seroconversion
Immunization status	Infants were allowed to receive routine childhood vaccinations according to local immunization practice during the study period, with a minimum interval of at least 7 days between the administration of routine vaccines and the study vaccine or placebo.
Location	Single site, China Medium-mortality country
Notes	**Date:** April to June 2010 **Source of funding:** GlaxoSmithKline **Study rationale:** To assess the safety of a single oral dose of HRV vaccine when compared to placebo group, in terms of solicited adverse events (AEs) in healthy infants aged 6-16 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment allocation at the investigator site was performed using an internet-based randomization system (SBIR)
Allocation concealment (selection bias)	Low risk	Treatment allocation at the investigator site was performed using an internet-based randomization system (SBIR)
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was conducted in a double-blind manner with respect to HRV vaccine and placebo. The parents/LARs of the infants, the study personnel and the investigator were unaware of the study vaccine administered (liquid HRV vaccine or placebo). The laboratory in charge of the laboratory testing was blinded to the treatment, and codes were used to link the participant and study (without any link to the treatment attributed to the participant) to each sample.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	Planned outcomes fully reported
Other bias	Low risk	No apparent other bias

RIX Li 2014-CHN

Study characteristics

Methods	RCT **Length of follow-up:** 2 years **Adverse event data collection methods:** (not reported if active or passive) serious adverse events were recorded throughout the study period.

RIX Li 2014-CHN *(Continued)*

Participants	**Number:** 3333 enrolled; 3148 evaluable **Age range:** 6 to 16 weeks **Inclusion criteria:** participants who the investigator believes that their parents/LARs can and will comply with the requirements of the protocol, male or female infant of Chinese origin between, and including, 6 and 16 weeks of age at the time of the first vaccination, healthy infants as established by medical history and clinical examination before entering into the study, born after a gestation period of 36 to 42 weeks inclusive **Exclusion criteria:** child in care; use of any investigational or non-registered product other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period; any clinically significant history of gastrointestinal disease; any confirmed or suspected immunosuppressive or immunodeficient condition; history of confirmed rotavirus gastroenteritis; acute disease and/or fever at the time of enrolment; gastroenteritis within 7 days preceding the study vaccine or placebo administration
Interventions	2 cohorts 1. 1st RV season RIX4414 (1575 participants) or placebo (1573 participants) 2. 2nd RV season RIX4414 (1500 participants) or placebo (1479 participants) **Schedule:** 2 doses of Rotarix™ vaccine, liquid formulation, at day 0 and at month 1
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause diarrhoea, severe and any severity 2. Rotavirus diarrhoea, severe and any severity 3. Rotavirus diarrhoea requiring hospitalization 4. All-cause mortality 5. Serious adverse events 6. Intussusception 7. Reactogenicity: fever, diarrhoea, vomiting 8. Adverse events requiring discontinuation 9. Dropouts before end of the trial **Outcomes to measure immunogenicity** 10. Seroconversion
Immunization status	As part of the routine childhood vaccination according to the Expanded Program of Immunization (EPI) recommendations in China, participants also received 3 doses of Infanrix™ vaccine and 3 doses of the oral poliovirus vaccine manufactured by the Institute of Medical Biology of the Chinese Academy of Medical Sciences (OPV). The Infanrix™ and the OPV vaccines were administered independently of (sub-cohort 1) or concomitantly with (sub-cohort 2) the Rotarix™ vaccine. When administered concomitantly, participants received the 3 doses of Infanrix™ vaccine at months 1, 2, and 3, and the 3 doses of the OPV vaccine at day 0, month 1 and month 2. The Rotarix™ and OPV vaccines were administered orally; the Infanrix™ vaccine was administered intramuscularly in the left anterolateral thigh.
Location	4 sites, China Medium-mortality country
Notes	**Date:** August 2010 to May 2012

RIX Li 2014-CHN *(Continued)*

Source of funding: GlaxoSmithKline

Study rationale: The aim of this study was to assess the efficacy, immunogenicity and safety of two doses of GSK Biologicals' HRV vaccine in healthy Chinese infants aged between 6 and 16 weeks at the time of the first dose of vaccination.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization sequence generated using software (MATEX developed for SAS)
Allocation concealment (selection bias)	Low risk	Treatment allocation at the investigator site was performed using SBIR (internet randomization tool).
Blinding (performance bias and detection bias) All outcomes	Low risk	Concealed from parents/guardians, study personnel, and investigators; placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition provided
Selective reporting (reporting bias)	Low risk	Planned outcomes fully reported
Other bias	Low risk	No apparent other bias

RIX Madhi 2010-AF

Study characteristics

Methods	RCT **Length of follow-up:** outcomes measured 2 weeks after last dose to 1 year of age, and at 2 years **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 Rotarix **Exclusion criteria:** children HIV-positive that were immunosuppressed at < 6 weeks before vaccination
Interventions	1. RIX4414 (Rotarix): 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

RIX Madhi 2010-AF *(Continued)*

Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause diarrhoea 2. Rotavirus diarrhoea: stool samples were tested for rotavirus with the use of an enzyme-linked immunosorbent assay (ELISA) (Rotaclone, Meridian Bioscience). 3. Severe rotavirus diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more*. 4. Severe all-cause diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more. 5. All-cause mortality: all deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age. 6. Serious adverse events: all serious adverse events were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age. **Outcomes to measure immunogenicity** 7. Immunogenicity: ELISA - 1 month after the last dose to determine the serum concentrations of antirotavirus IgA antibody
Immunization status	Vaccines that are administered routinely according to the guidelines of the Expanded Programme on Immunization (EPI) were concomitantly administered with the vaccine or placebo, including oral polio vaccine.
Location	South Africa and Malawi High-mortality countries
Notes	This trial was conducted in Malawi and South Africa, with data reported separately by country available under RIX Madhi 2010-MWI and RIX Madhi 2010-ZAF. **Date:** October 2005 to February 2007 (South Africa); October 2006 to July 2007 (Malawi) **Source of funding:** PATH Rotavirus Vaccine Programme and GlaxoSmithKline

Risk of bias

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) All outcomes	Low risk	The site investigator was unaware of the group assignments of the children.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups

RIX Madhi 2010-AF *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent other bias

RIX Madhi 2010-MWI

Study characteristics	
Methods	RCT **Length of follow-up:** outcomes measured 2 weeks after last dose to 1 year of age, and at 2 years **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:** 1773 enrolled **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 Rotarix **Exclusion criteria:** children HIV-positive that were immunosuppressed at < 6 weeks before vaccination
Interventions	1. RIX4414 (Rotarix): dose same as commercial; 1182 participants 1.1 2 doses 1.2 3 doses 2. Placebo: 591 participants 2.1 Normal placebo **Schedule:** 2 to 3 doses given 1 month apart
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause diarrhoea 2. Rotavirus diarrhoea: stool samples were tested for rotavirus with the use of an ELISA (Rotaclone, Meridian Bioscience). 3. Severe rotavirus diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more*. 4. Severe all-cause diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more. 5. All-cause mortality: all deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age. 6. Serious adverse events: all serious adverse events were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age. **Outcomes to measure immunogenicity** 7. Immunogenicity: ELISA - 1 month after the last dose to determine the serum concentrations of antirotavirus IgA antibody

RIX Madhi 2010-MWI *(Continued)*

Immunization status	Vaccines that are administered routinely according to the guidelines of the Expanded Programme on Immunization (EPI) were concomitantly administered with the vaccine or placebo, including oral polio vaccine.
Location	Malawi High-mortality country
Notes	This trial was conducted in Malawi and South Africa. This part presents data reported for the Malawi cohort, while data reported for South Africa can be found under RIX Madhi 2010-ZAF, and data reported for both countries under RIX Madhi 2010-AF. **Date:** October 2006 to July 2007 **Source of funding:** PATH Rotavirus Vaccine Programme and GlaxoSmithKline

Risk of bias

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 randomizations block size.
Blinding (performance bias and detection bias) All outcomes	Low risk	The site investigator was unaware of the group assignments of the children.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent other bias

RIX Madhi 2010-ZAF

Study characteristics

Methods	RCT **Length of follow-up:** outcomes measured 2 weeks after last dose to 1 year of age, and at 2 years (only cohort 2) **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:** 3166 enrolled **Age range:** 1 to 6 months

RIX Madhi 2010-ZAF *(Continued)*

	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 Rotarix **Exclusion criteria:** children HIV-positive that were immunosuppressed at < 6 weeks before vaccination
Interventions	1. RIX4414 (Rotarix): dose same as commercial; 2116 participants 1.1 2 doses 1.2 3 doses 2. Placebo: 1050 participants 2.1 Normal placebo **Schedule:** 2 to 3 doses given 1 month apart
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause diarrhoea 2. Rotavirus diarrhoea: stool samples were tested for rotavirus with the use of an ELISA (Rotaclone, Meridian Bioscience). 3. Severe rotavirus diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more*. 4. Severe all-cause diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more. 5. All-cause mortality: all deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age. 6. Serious adverse events: all serious adverse events were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age. **Outcomes to measure immunogenicity** 7. Immunogenicity: ELISA - 1 month after the last dose to determine the serum concentrations of antirotavirus IgA antibody *G types for severe rotavirus diarrhoea for the first year follow-up were reported and added to the analyses; G types for any rotavirus diarrhoea were reported for the second year only, and were not added to the analysis.
Immunization status	Vaccines that are administered routinely according to the guidelines of the Expanded Programme on Immunization (EPI) were concomitantly administered with the vaccine or placebo, including oral polio vaccine.
Location	South Africa High-mortality country
Notes	This trial was conducted in Malawi and South Africa. This part presents data reported for the South Africa cohorts; data reported for Malawi can be found under RIX Madhi 2010-MWI, and data reported for both countries under RIX Madhi 2010-AF. **Date:** October 2005 to February 2007 **Source of funding:** PATH Rotavirus Vaccine Programme and GlaxoSmithKline
Risk of bias	

RIX Madhi 2010-ZAF *(Continued)*

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) All outcomes	Low risk	The site investigator was unaware of the group assignments of the children.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent other bias

RIX Narang 2009-IND

Study characteristics	
Methods	RCT **Length of follow-up:** 1 month after dose 2 **Adverse event data collection methods:** passive; parents/guardians filled in diary cards of any symptoms.
Participants	**Number:** 363 enrolled; 344 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy male or female infants 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 **Exclusion criteria**: history of confirmed rotavirus gastroenteritis or with prior administration of experimental rotavirus vaccine
Interventions	1. RIX4414 (Rotarix): $10^{6.5}$ PFU; 182 participants (randomized) 2. Placebo: 181 participants (randomized) **Schedule:** 2 oral doses given at age 2 and 4 months
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 8-day (days 0 to 7) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 31 days (days 0 to 30) after each dose, according to MedDRA classification; measured up to 31 days after vaccine/placebo

RIX Narang 2009-IND *(Continued)*

	2. Serious adverse events: no definition; occurrence throughout entire study period (up to 31 days after vaccine/placebo) 3. Dropouts: no definition; measured up to 31 days after vaccine/placebo 4. Rotavirus diarrhoea: presence of rotavirus in gastroenteritis episode stools collected from dose 1 of Rotarix vaccine/placebo up to 2 months after dose 2; measured up to 31 days after vaccine/placebo 5. All-cause death 6. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 7. Seroconversion: appearance of anti-rotavirus immunoglobulin A (IgA) antibody concentration ≥ 20 U/mL in participants who were seronegative before vaccination (review included data from 1 month after dose 2)
Immunization status	Routine vaccinations (diphtheria-tetanus-whole cell pertussis-hepatitis b, *H. influenzae* type b, and oral poliovirus vaccine) were administered at 6, 10, and 14 weeks of age (given with a 2-week separation from the first and subsequent dose of the Rotarix vaccine or placebo)
Location	4 centres in India High-mortality country
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 human rotavirus vaccine in healthy infants in India"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS program
Allocation concealment (selection bias)	Low risk	Likely to be adequate: treatment masked to investigators Quote: "a treatment number identified uniquely the vaccine doses to be administered to the same subject" and "subjects were administered the vaccine dose with the lowest treatment number available at the study centre".
Blinding (performance bias and detection bias) All outcomes	Low risk	Parent/guardian and study personnel were not aware of the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusions balanced between groups
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported
Other bias	Low risk	No apparent other bias

RIX NCT00158756-RUS

Study characteristics	
Methods	RCT **Length of follow-up:** 1 year **Adverse event data collection methods:** Not reported
Participants	**Number:** 308 enrolled; 209 evaluated (1 study arm was not included in analyses of this review) **Age range:** 11 to 17 weeks of age at the time of the first vaccination **Inclusion criteria:** infants who the investigator believes that their parent/guardian can and will comply with the requirements of the protocol, administration of 1 dose of hepatitis B vaccine at birth, male or female between and including 11 and 17 weeks of age at the time of the first DTPw vaccination, free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria**: 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 planned use during the study period, chronic administration of immunosuppressants or other immune-modifying drugs since birth, any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required), administration of immunoglobulins or any blood products, or both, since birth or planned administration during the study period
Interventions	1. Rotarix at 3 and 4½ months + DTPw-HBV at 3, 4½ and 6 months (80 participants) 2. Placebo at 3 and 4½ months + DTPw-HBV at 3, 4½ and 6 months (25 participants) 3. Rotarix at 3 and 4½ months + DTPw-HBV Kft. at 3, 4½ and 6 months (81 participants) 4. Placebo at 3 and 4½ months + DTPw-HBV Kft. at 3, 4½ and 6 months (23 participants) 5. DTPwcsl + HBV at 3, 4½ and 6 months (99 participants); this group was not included in analyses of this review.
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity 2. Serious adverse events 3. All-cause death 4. Intussusception 5. Dropouts **Outcomes to measure immunogenicity** 6. Seroconversion
Immunization status	GlaxoSmithKline (GSK) Biologicals' Tritanrix™HepB and GSK Biologicals Kft's DTPwHBV Vaccines as compared to concomitant administration of Commonwealth Serum Laboratory's (CSL's) DTPw (Triple Antigen™) and GSK Biologicals' HBV (Engerix™B), when co-administered with GSK Biologicals' oral live attenuated Human Rotavirus (HRV) vaccine, to healthy infants at 3, 4½ and 6 months of age, after a birth dose of Hepatitis B vaccine
Location	9 sites, Russian Federation Medium-mortality country

RIX NCT00158756-RUS *(Continued)*

Notes	**Date:** September 2005 to November 2006 **Source of funding:** GlaxoSmithKline **Study rationale:** To compare the 2 formulations of GSK Biologicals' DTPw-HBV vaccine to concomitant administration of CSL's DTPw vaccine and GSK Biologicals' HBV with respect to the antibody response to the diphtheria antigen after a 3-dose primary vaccination course.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized (4:1:4:1:5) using GSK Biologicals central randomization system (SBIR)
Allocation concealment (selection bias)	Low risk	Cental allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was conducted in a double-blind manner with respect to the Rotarix and placebo groups and in single-blinded manner with respect to the Tritanrix-HepB and Zilbrix groups. The study was open with respect to the Triple Antigen + Engerix-B group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No apparent other bias

RIX Omenaca 2012-EU

Study characteristics

Methods	RCT **Length of follow-up:** 30 to 83 days after dose 2 **Adverse events data collection methods:** active surveillance: at each study visit parents were asked about AEs; passive surveillance: throughout the trial, parents were asked to immediately report AEs to the investigator.
Participants	**Number:** 1009 **Age range:** 6 to 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 human rotavirus vaccine/placebo administration **Exclusion criteria:** use of any investigational or non-registered product (drug or vaccine) other than the human rotavirus vaccine within 30 days preceding the first dose of human rotavirus 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

RIX Omenaca 2012-EU *(Continued)*

	Each study group was further stratified into 2 subgroups depending on the gestational age at birth of the participant: Stratum I: very pre-term infants, born after a gestational period of 27 to 30 weeks (189 to 216 days) (20% of enrolment); Stratum II: mild pre-term infants born after a gestational period of 31 to 36 weeks (217 to 258 days) (80% of enrolment).
Interventions	1. Rotarix, 670 participants 2. Placebo, 339 participants **Schedule:** 2 oral doses of vaccine or placebo, 1 dose at day 0 and 1 dose at months 1 or 2, depending on the country
Outcomes	**Clinical outcome measures** 1. Serious adverse events, including fatal events and intussusception, from day 0 up to 83 days after dose 2 of Rotarix vaccine/placebo 2. Solicited symptoms, within 15 days after each Rotarix vaccine/placebo dose. Solicited symptoms included diarrhoea (3 or more looser than normal stools/day), fever (axillary temperature over 37.5 °C), irritability, loss of appetite, and vomiting. 3. All-cause gastroenteritis and rotavirus gastroenteritis, from dose 1 up to 83 days after dose 2 of Rotarix vaccine/placebo. Gastroenteritis: diarrhoea with or without vomiting. Rotavirus gastroenteritis: a gastroenteritis episode was a rotavirus gastroenteritis episode if a stool sample taken during or not later than 7 days after the episode was rotavirus positive by ELISA. 4. Dropouts before the end of the trial **Outcomes to measure immunogenicity** 5. Seroconversion to anti-rotavirus IgA antibody, at visit 3, 1 month after dose 2 of Rotarix vaccine/placebo. Number of participants with anti-rotavirus IgA antibody concentration over 20 units/mL
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 2 days from each other) with each human rotavirus vaccine or placebo dose. Hepatitis B and BCG vaccines 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 infant's study participation: • Vaccine against *S. pneumoniae* (Prevenar®) in France and Spain (concomitantly with human rotavirus vaccine/placebo) • Vaccine against *Neisseria meningitidis* (Neis Vacc C®) is allowed if there is at least a 14-day interval with respect to the administration of the human rotavirus vaccine/placebo.
Location	France, Poland, Portugal, Spain Low-mortality countries
Notes	Study known as *RV1 NCT00420745 2009-EU* in previously published versions of this review **Date:** January 2007 to March 2008 **Source of funding:** GlaxoSmithKline **Registration number:** NCT00420745

RIX Omenaca 2012-EU *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomization
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Parent/guardian and study personnel were not aware of the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced between groups
Selective reporting (reporting bias)	Low risk	All expected outcomes included
Other bias	Low risk	No apparent other bias

RIX Phua 2005-SGP

Study characteristics	
Methods	RCT **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	1. RIX4414 (Rotarix) 1.1. $10^{4.7}$ 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

RIX Phua 2005-SGP *(Continued)*

	Outcomes measured at ~15 months (efficacy data from 2 weeks after second dose to 18 months of age)
Outcomes	**Clinical outcome measures** 1. All-cause diarrhoea: episodes of acute gastroenteritis; parents instructed to record (diary cards) body temperature, the number of episodes of vomiting, the number of looser-than-normal stools, and whether they sought medical intervention or medication, and were asked to obtain at least 2 stool samples on 2 different days within 7 days of the onset of symptoms; measured at 2 weeks to 18 months 2. Rotavirus diarrhoea: see all-cause diarrhoea; "Rotavirus gastroenteritis was confirmed if at least 1 of the 2 stool specimens was found to be positive for rotavirus by ELISA. Rotavirus isolates were G-typed by use of reverse-transcriptase polymerase chain reaction (RT-PCR)"; measured at 2 weeks to 18 months. 3. Severe all-cause diarrhoea: severity of each episode of gastroenteritis graded using a 20-point scoring system described by Ruuska 1990 4. Severe rotavirus diarrhoea: see severe all-cause diarrhoea 5. All-cause death 6. All-cause hospital admission 7. Emergency department visit 8. Serious adverse events 9. Reactogenicity: fever if rectal temperature > 38 °C 10. Adverse events requiring discontinuation 11. Rotavirus diarrhoea requiring hospitalization 12. Dropouts **Outcomes to measure immunogenicity** 11. Shedding of vaccine virus: in stool samples on day of each vaccination and on days 7 and 15 after each vaccination (from 50 participants/group, the "stool sample subset") (review included data from 1 month after dose 1 and 1 month after dose 2) 12. Seroconversion: serum anti-rotavirus IgA antibody seroconversion rate; "seroconversion" "defined by an anti-rotavirus IgA antibody concentration of ≥ 20 U/mL, for infants who were initially (i.e. before administration of the first vaccine dose) seronegative for anti-rotavirus IgA antibodies (i.e. a concentration of < 20 U/mL) and/or who had a stool sample that was negative for rotavirus antigen. Any detection of RIX4414 antigen in stool samples was taken as evidence of a vaccine response".
Immunization status	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, poliovirus, and *H. influenzae* type b co-administered with interventions
Location	8 centres in Singapore Low-mortality country
Notes	**Date:** 4 January 2001 to 15 April 2003 **Funding:** GlaxoSmithKline Biologicals **Other:** 93% of population were Asian.

Risk of bias

Bias	Authors' judgement	Support for judgement

RIX Phua 2005-SGP *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS program
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Parent/guardian and study personnel were not aware of the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	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	Low risk	No apparent other bias

RIX Phua 2009-AS

Study characteristics	
Methods	RCT **Length of follow-up:** 2 weeks post-dose 2 to 3 years **Adverse events data collection methods:** passive method, using diary cards
Participants	**Number:** 10,708 enrolled; 10,519 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:** "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	1. RIX4414 (Rotarix) 10^6 FFU; 5359 participants 2. Placebo; 5349 participants All vaccines given in 2 doses with a 1 to 2-month interval
Outcomes	**Clinical outcome measures**

RIX Phua 2009-AS *(Continued)*

	1. All-cause diarrhoea: a gastroenteritis episode was defined as occurrence of diarrhoea with or without vomiting (diarrhoea was defined as the passage of 3 or more looser-than-normal stools within a 24-hour period). 2. Severe all-cause diarrhoea: severe gastroenteritis was defined as an episode of diarrhoea with or without vomiting that required overnight hospitalization or rehydration therapy, or both (equivalent to WHO plan B or C) in a medical facility and with a score of 11 points on the 20-point Vesikari scale. 3. Rotavirus diarrhoea: stool samples collected during gastroenteritis episodes were tested for the presence of rotavirus using ELISA method (Rotaclone™, Meridian Bioscience) at GlaxoSmithKline Biologicals' laboratories in Rixensart, Belgium. All rotavirus-positive stool samples were tested by reverse transcriptase polymerase chain reaction (RT-PCR) followed by reverse hybridization assay, and optional sequencing, at Delft Diagnostic Laboratory, The Netherlands, to determine G and P types, and differentiation of G1P[8] vaccine type. 4. Severe rotavirus diarrhoea*: see above 5. Emergency department visit: active surveillance was conducted at hospitals and medical facilities in the study area to capture gastroenteritis episodes requiring hospitalization and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility from day of the first vaccine or placebo dose until the follow-up visit at 24 months of age. 6. Serious adverse events: intussusception and SAEs were followed during the study duration. A case of definite intussusception required confirmation at surgery or autopsy or by using imaging techniques such as gas or liquid contrast enema or abdominal ultrasound. Abstractable data for all serious adverse events and Kawasaki disease were only provided for the third year of follow-up. Intussusception data for the third year follow-up were not included in the analysis as the follow-up population was smaller (Rotarix: 2/4272; placebo: 1/4226) 7. All-cause deaths **Outcomes to measure immunogenicity** None *G types for severe rotavirus diarrhoea up to two years follow-up w[ere] reported and added to the analyses, data for the third year w[ere] reported but not included in the analysis as the follow-up population was smaller".
Immunization status	Infants received other routine paediatric immunizations (combined diphtheria toxoid-tetanus toxoid-acellular pertussis (DTPa) inactivated poliovirus (IPV) and *H. influenzae* type b (HiB) vaccine and hepatitis B vaccine (HBV)) during the study period according to local schedules. Almost all infants received BCG dose at birth. If oral polio vaccine (OPV) was given as part of the routine schedule in the participating countries, a time interval of 2 weeks was observed between the OPV doses and RIX4414 vaccine/placebo doses. One dose of oral polio vaccine (OPV) was given at birth in Hong Kong (99.8% participants) and Taiwan (0.7% participants). However, during the study period, > 95% of infants in the 3 countries received DTPa-IPV-HiB concomitantly with both doses of RIX4414 vaccine/placebo as per local schedules. 50.9% of participants were male and the study population was predominantly Chinese (76.3%).
Location	Hong Kong, Singapore, Taiwan Low-mortality countries
Notes	**Date:** 8 December 2003 to 31 August 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	

RIX Phua 2009-AS *(Continued)*

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® program and was used to number the vaccines.
Allocation concealment (selection bias)	Low risk	A randomization blocking scheme was used to ensure that the balance between treatments was maintained. Treatment allocation at the investigator sites was performed using a central randomization system on the Internet.
Blinding (performance bias and detection bias) All outcomes	Low risk	Data analysis was performed at GSK Biologicals. The treatment code remained masked, except for statisticians and the database administrator.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary analysis of efficacy was performed from 2 weeks post-dose 2 until 2 years of age on the ATP cohort that included participants who completed the full 2-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	Low risk	No apparent other bias

RIX Rivera 2011-DOM

Study characteristics	
Methods	RCT **Length of follow-up:** 17 weeks **Adverse events data collection methods:** not reported
Participants	**Number:** 200 **Age range:** 6 to 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 infant
Interventions	1. Rotarix (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:** 1 complimentary dose of Rotarix was administered to all infants enrolled in this study (both study groups) who were aged less than 6 months at visit 3 (week 13) as a benefit to the placebo group for participation in the study
Outcomes	**Clinical outcome measures (safety and efficacy)**

RIX Rivera 2011-DOM *(Continued)*

	1. Gastroenteritis, up to week 17 2. Rotavirus gastroenteritis, up to week 13. Rotavirus gastroenteritis episodes were defined as gastroenteritis episodes for which the stool sample temporally closest to the onset day of the gastroenteritis episode was positive for rotavirus by ELISA. 3. Serious adverse events, including fatal serious adverse events and intussusception, up to week 17 4. Dropouts from the study **Outcomes to measure immunogenicity** 5. Anti-rotavirus IgA antibody seroconversion and concentration in each group, at visit 3
Immunization status	All infants received 3 doses of combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus and *H. influenzae* vaccine.
Location	Dominican Republic High-mortality country
Notes	Study known as *RV1 NCT00396630 2009-LA* in previously published versions of this review. **Date:** January 2007 to February 2008 **Source of funding:** GlaxoSmithKline **Registration number:** NCT00396630 **Aim:** "to explore horizontal transmission of the HRV [human rotavirus] vaccine strain within a family from the twin vaccinated with Rotarix to the twin receiving placebo"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization list was generated at GlaxoSmithKline (GSK) Biologicals, Rixensart, using a standard SAS® program. A randomization blocking scheme (1:1 ratio, block size = 2) was used to ensure balance between the treatment arms; a treatment number uniquely identified the vaccine doses to be administered to the same infant".
Allocation concealment (selection bias)	Low risk	Quote: "No investigator or any person involved in the clinical trial (including laboratory personnel, statisticians and data management) was aware of the treatment groups during the course of the study".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The study was double-blinded and the parents/guardians of infants, investigator and the study personnel were unaware of the study vaccine administered".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusions balanced between groups
Selective reporting (reporting bias)	Low risk	Trial report did not provide enough details.
Other bias	Low risk	No apparent other bias

RIX Ruiz-Palac 06-LA/EU

Study characteristics	
Methods	RCT **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 Rotarix 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 HIV infection; history of allergic disease or reaction likely to be exacerbated by any component of the vaccine; administration of immunoglobulins or blood products or both 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	1. RIX4414 (Rotarix): $10^{6.5}$ 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
Outcomes	**Clinical outcome measures** 1. Serious adverse events: "defined as any new health-related problems that resulted in death, were life-threatening, necessitated hospitalization or prolongation of existing hospitalization, or resulted in disability or incapacity"; "case of definite intussusception required confirmation at surgery or autopsy or with the use of imaging techniques, such as imaging with gas- or liquid-contrast enema or abdominal ultrasonography"; measured up to 30 days after vaccination and during the first year follow-up for efficacy; intussusception measured up to 100 days after dose 1. Final intussusception results taken from CDC report (CDC 2010) 2. Severe all-cause diarrhoea: severe gastroenteritis measured as an "episode of diarrhoea with or without vomiting that required hospitalization and/or re-hydration therapy (equivalent to WHealth O plan B or C) in a medical facility"; measured from 2 weeks after second dose up to 2 years follow-up 3. All-cause diarrhoea; measured from 2 weeks after second dose up to 2 years follow-up 4. Rotavirus diarrhoea; measured from 2 weeks after second dose up to 2 years follow-up 5. Severe rotavirus diarrhoea: severe rotavirus gastroenteritis defined as an "an episode of severe gastroenteritis occurring at least 2 weeks after the full vaccination course in which rotavirus other than

RIX Ruiz-Palac 06-LA/EU *(Continued)*

	vaccine strain was identified in a stool sample collected during the episode of severe gastroenteritis"; measured from 2 weeks after second dose up to 2 years follow-up 6. All-cause death; measured up to 30 days after vaccination 7. All-cause hospital admission; from 2 weeks after second dose up to 2 years follow-up 8. Reactogenicity; up to 30 days after vaccination 9. Dropouts; measured up to 2 years follow-up 11. Rotavirus diarrhoea requiring hospitalization 12. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 13. Seroconversion: serum rotavirus IgA antibody concentrations in a subset of 100 participants per country (except in Finland) at visits 1 and 3 (data not included in review because it was not a random sample) Outcomes measured up to 30 days after second dose of vaccine (safety outcomes) and up to 2 years (efficacy outcomes)
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 Low-mortality: Finland; Medium-mortality countries: Argentina, Brazil, Chile, Colombia, Mexico, Panama, Peru; High-mortality countries: Dominican Republic, Honduras, Nicaragua, 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "GlaxoSmithKline Biologicals provided vaccine supplies that were numbered with a computer-generated randomization list. We used a blocking scheme randomization. GSK did the masking and concealment".
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was done by a central Internet randomization system".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "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) All outcomes	Low risk	Quote: "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.

RIX Ruiz-Palac 06-LA/EU *(Continued)*

Other bias	Low risk	No apparent other bias

RIX Salinas 2005-LA

Study characteristics	
Methods	RCT **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 *H. 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	1. RIX4414 (Rotarix) 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 Rotarix x placebo to receive 3 doses. This was not mentioned in the main publication, only in the GlaxoSmithKline report (no data available).
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events: no definition; measured during follow-up (2 years) 2. Reactogenicity: no definition; measured up to 43 days after vaccination 3. All-cause diarrhoea: gastroenteritis defined as diarrhoea characterized by ≥ 3 looser-than-normal stools within a day; minimum of 5 days required between episodes for them to be considered as separate events; measured during follow-up (2 years) 4. Severe all-cause diarrhoea: information on diary cards was used to assess the severity of each gastroenteritis episode according to a 20-point scoring system; measured during follow-up (2 years) 5. Rotavirus diarrhoea: all rotavirus-positive specimens were tested by RT-PCR at GlaxoSmithKline to determine the G type; any G1 rotavirus detected until 2 months after the second dose were analysed to differentiate between vaccine strain and wild G1 strains; only gastroenteritis episodes in which wild rotavirus other than the vaccine strain was identified in a stool specimen were included in the efficacy analysis; measured during follow-up (2 years)

RIX Salinas 2005-LA *(Continued)*

	6. Severe rotavirus diarrhoea: see above; measured during follow-up (2 years) 7. All-cause hospital admission: no definition; measured during follow-up (2 years) 8. All-cause mortality: no definition; measured during follow-up (2 years) 9. Rotavirus diarrhoea resulting in hospitalization **Outcomes to measure immunogenicity** 10. Vaccine take: rotavirus shedding in stool specimens (review includes data from day 7 after dose 2) 11. Seroconversion: "percentages of infants with post-antirotavirus IgA antibody concentration 20 units/mL in infants who were negative for rotavirus before the first dose of RIX4414 or placebo" (review included data from 2 months after dose 1 and 2 months after dose 2)
Immunization status	Oral polio vaccine given after 2 weeks, not together with Rotarix
Location	Brazil, Mexico, Venezuela Medium- (Brazil, Mexico) and High-mortality (Venezuela) countries
Notes	**Date:** 25 May 2001 to 8 November 2003 **Source of funding:** GlaxoSmithKline Biologicals **Malnutrition:** reported in *Journal of Infectious Disease*, 2007, 196(4): 537-40 **Other:** main publication did not report that the trial included 2 subsets: • 2 doses of human rotavirus or placebo subset: these participants received 2 oral doses of Rotarix vaccine or placebo according to a 0-, 2-month schedule, and routine vaccinations (DTPw- Hepatitis B vaccine (HBV) + Hib vaccine) at a 0-, 2-, and 4-months schedule. • 3 doses of Rotarix or placebo subset: these participants received 3 oral doses of Rotarix vaccine or placebo, and routine vaccinations (DTPw-HBV + Hib vaccine) concomitantly with each dose of human rotavirus vaccine and placebo at a 0-, 2-, and 4-months schedule. **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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated Quote:"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)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blinding was maintained during the entire study period".
Incomplete outcome data (attrition bias)	Low risk	Missing data balanced across groups

RIX Salinas 2005-LA *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Not all prespecified 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.

RIX Steele 2008-ZAF

Study characteristics	
Methods	RCT **Length of follow-up:** up to 6 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 2 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 immunosuppressed individual or pregnant woman. 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	1. RIX4414 (Rotarix): 10^5 FFU; 2 doses given 1 month apart; 300 participants (randomized) 1.1. Rotarix vaccine + oral polio vaccine + diphtheria-tetanus-acellular pertussis/*H. influenzae* type b vaccine 1.2. Rotarix vaccine + oral polio vaccine placebo + diphtheria-tetanus-acellular pertussis inactivated polio-*H. influenzae* type b vaccine 1.3. Rotarix placebo + diphtheria-tetanus-acellular pertussis inactivated polio/*H. influenzae* type b vaccine 2. Placebo: 2 doses given 1 month apart; 150 participants (randomized)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity (see **Adverse event data collection methods** above)

RIX Steele 2008-ZAF *(Continued)*

	2. Serious adverse events: Infants who experienced a serious adverse event and required hospitalization were admitted at the local district hospital in the study sites or at Ga-Rankuwa Hospital, the referral hospital for the study site and surrounding areas. Parents were informed on the symptoms of intussusception and were instructed to contact the study physician or clinic if any signs of intussusception became apparent. Any suspected cases were immediately referred to Ga-Rankuwa Hospital. All serious adverse events were reported to the sponsor and the Ethics committees and followed up until resolved. Parents were contacted 6 months after the second dose of RIX4414 or placebo to obtain information on any serious adverse events since the final study visit. All serious adverse events were reviewed periodically by an independent safety monitoring committee. 3. All-cause death 4. Dropouts 5. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 6. Vaccine virus shedding: vaccine virus in stool sample (review included data from combined time points) 7. Seroconversion: appearance of anti-rotavirus IgA antibody (concentration ≥ 20 U/mL) in participants negative for rotavirus before vaccination (review included data from 289 participants)
Immunization status	Diphtheria-tetanus-acellular pertussis, polio virus, and *H. influenzae* type b co-administered in trial
Location	Madibeng District, North West Province, South Africa High-mortality country
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 WHO, 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Very likely Quote: "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 WHO, 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)	Low risk	Likely to be adequate: treatment masked to investigators Quote: "a unique randomization number identified the vials to be administered to the same subject" and "subjects were administered the vaccine dose with the lowest treatment number available at the study centre".
Blinding (performance bias and detection bias)	Unclear risk	Blinding of oral polio vaccine co-administration not completely blinded

RIX Steele 2008-ZAF *(Continued)*

All outcomes		Quote: "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) All outcomes	Low risk	Quote: "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 prespecified outcomes reported
Other bias	Low risk	No apparent other bias

RIX Steele 2010a-ZAF

Study characteristics	
Methods	RCT **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 post-vaccination 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 a day (diarrhoea), ≥ 3 episodes of vomiting a 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 a day (diarrhoea), 2 episodes of vomiting a day (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 gastroenteritis or previous documented rotavirus gastroenteritis.
Interventions	1. Rotarix: 3 doses at least $10^{6.0}$ $CCID_{50}$ viral concentration 2. Placebo
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity (see **Adverse event data collection methods** above) 2. All-cause diarrhoea; A gastroentiritis episode was defined as diarrhoea (3 or more, looser-than-normal stools a day) with or without vomiting. Stool samples were collected on days 0, 7, 15, and 22 of doses 1 and 2 and on days 0, 7, 15, 30, 45, and 60 of dose 3.

RIX Steele 2010a-ZAF *(Continued)*

	3. Rotavirus diarrhoea; measured from 1 week after second dose up to 2 months' follow-up 4. Serious adverse events: infants who experienced a serious adverse event and required hospitalization were admitted at the local district hospital in the study sites or at Ga-Rankuwa Hospital, the referral hospital for the study site and surrounding areas. Parents were informed on the symptoms of intussusception and were instructed to contact the study physician or clinic if any signs of intussusception became apparent. Any suspected cases were immediately referred to Ga-Rankuwa Hospital. All serious adverse events were reported to the sponsor and the Ethics committees and followed up until resolved. Parents were contacted 6 months after the second dose of RIX4414 or placebo to obtain information on any serious adverse events since the final study visit. All serious adverse events were reviewed periodically by an independent safety monitoring committee. 5. All-cause death 6. Dropouts **Outcomes to measure immunogenicity** 7. Vaccine take: defined as serum antirotavirus IgA concentration 20 U/mL in post-vaccination sera or rotavirus vaccine shedding in any stool sample collected from dose 1 to 2 months post-dose 3 for infants initially negative for rotavirus 8. Seroconversion: appearance of anti-rotavirus IgA antibody (concentration ≥ 20 U/mL) in participants negative for rotavirus before vaccination (review included data from 289 participants)
Immunization status	Rotarix vaccine was concomitantly administered with 3 doses of combined diphtheria, tetanus and whole-cell pertussis, hepatitis B, and *H. influenzae* type b vaccine (TritanrixHepBHib) and OPV (PolioSabin)
Location	Pretoria, South Africa High-mortality country
Notes	**Registration number:** ISRCTN11877362/NCT00263666 **Source of funding:** RAPID trials (USA); WHO (Switzerland) and GlaxoSmithKline Biologicals For infants who developed clinical symptoms of HIV (WHO stages III or IV disease) any time after enrolment, access to antiretroviral therapy (cotrimoxazole) according to the South African national guidelines was facilitated. Infants who needed treatment were referred to antiretroviral therapy centres by the investigators.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Very likely Quote: "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 WHO, 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 randomization; no further details

RIX Steele 2010a-ZAF *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "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) All outcomes	Low risk	Quote: "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 prespecified outcomes reported
Other bias	Low risk	No apparent other bias

RIX Steele 2010b-ZAF

Study characteristics	
Methods	RCT **Length of follow-up:** up to 6 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. 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	1. RIX4414 (Rotarix): at least $10^{6.0}$ PFU $CCID_{50}$ 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.
Outcomes	**Clinical outcome measures (safety and efficacy)**

RIX Steele 2010b-ZAF *(Continued)*

	1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 15-day (days 0 to 14) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 43 days (days 0 to 42) after each dose, according to MedDRA classification; measured up to 43 days after vaccine/placebo 2. Serious adverse events: occurrence throughout entire study period; measured up to 6 months 5. All-cause death: fatal adverse events measured up to 6 months 6. Dropouts: measured up to 6 months 7. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 8. Viral shedding: presence of rotavirus in any stool sample (review included data from combined time points (these combined data for 2 and 3 doses)) 9. Seroconversion: appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/mL in participants negative for rotavirus before first dose (review included data from 1 month after dose 1 and 2 months after dose 3)
Immunization status	Infants received routine vaccinations according to the local EPI schedule in South Africa. BCG and OPV vaccinations were given at birth; all other routine vaccinations (including diphtheria-tetanus toxoids-whole cell pertussis, hepatitis B, *H. influenzae* type b, and OPV) were administered concomitantly with the study vaccine. 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 High-mortality country
Notes	Study known as *RV1 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

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)	Low risk	Likely to be adequate: treatment masked to investigators Quote: "a randomization number uniquely identified the three vials to be administered to the same subject" and "subjects were administered the vaccine dose with the lowest number available at the study centre".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "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) All outcomes	Low risk	Quote: "All infants who had received at least one dose of RIX4414 or placebo (total vaccinated cohort) were included in the primary analysis of reactogenicity".

RIX Steele 2010b-ZAF *(Continued)*

Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No apparent other bias

RIX Tregnaghi 2011-LA

Study characteristics	
Methods	RCT **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:** boys or girls 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	1. RIX4414 (Rotarix): $10^{6.5}$ 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 Rotarix 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
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea: occurrence of severe rotavirus gastroenteritis (requiring hospitalizations or rehydration therapy or both in a medical facility) caused by the wild rotavirus strains during the period starting from 2 weeks after dose 2 until 1 year of age; measured up to 1 year after vaccine/placebo 2. Serious adverse events: occurrence throughout the entire study period; measured up to 1 year after vaccine/placebo 3. Dropouts: measured up to 1 year after vaccine/placebo 4. All-cause death: fatal serious adverse events; measured up to 1 year after vaccine/placebo 5. Adverse events resulting in discontinuation 6. All-cause diarrhoea – severe

RIX Tregnaghi 2011-LA *(Continued)*

	Outcomes to measure immunogenicity 7. Seroconversion: serum rotavirus immunoglobulin A (IgA) antibody concentrations 1 to 2 months after second study vaccine dose (at visit 3) in a subset of 300 participants enrolled in year 2003 - 2004 (review included data from 1 to 2 months after dose 2)
Immunization status	All participants received routine infant vaccinations (Hepatitis B vaccine), diphtheria-tetanus-acellular pertussis, poliovirus, and *H. 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 Rotarix 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 six countries in Latin America Medium- (Argentina, Brazil, Colombia, Panama) and High-mortality (Dominican Republic, Honduras) countries
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 human rotavirus [Rotarix] vaccine given concomitantly with routine EPI vaccinations (including DT-Pw [licensed combined diphtheria and tetanus toxoids and whole-cell pertussis vaccine], HBV [licensed hepatitis type B vaccine], Hib [licensed *H. influenzae* type b vaccine] and OPV [oral polio vaccine]) in healthy infants"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS program
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Parent/guardian and study personnel were not aware of the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	Low risk	96.7% completed the study.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Unclear risk	No details

RIX Vesikari 2004a-FIN

Study characteristics

Methods	RCT

RIX Vesikari 2004a-FIN *(Continued)*

	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	1. RIX4414 (Rotarix) 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 Rotarix 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.
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Adverse events requiring discontinuation: no definition; measured at 31-day follow-up after each dose 2. Serious adverse events: no definition; measured at 31-day follow-up after each dose 3. Reactogenicity: no definition; measured at 31-day follow-up after each dose 4. Dropouts: no definition; measured at 31-day follow-up after each dose 5. All-cause mortality: no definition; measured at 31-day follow-up after each dose **Outcomes to measure immunogenicity** 6. Rotavirus shedding in stool (review included data from day 7 to 9 after dose 2) 7. Seroconversion: appearance of serum anti-rotavirus IgA antibody to rotavirus in post-vaccination sera at a titre of ≥ 20 U/mL in previously uninfected infants; measured in infants only (review included data from 2 months after dose 1 and 1 month after dose 2)
Immunization status	Infant routine vaccinations were separated from the study vaccines by 2 weeks.
Location	2 centres in Finland Low-mortality country

RIX Vesikari 2004a-FIN *(Continued)*

Notes	**Date:** 29 May to 18 December 2000 **Source of funding:** GlaxoSmithKline Biologicals Trial report also included results for a study in adults and in previously rotavirus-infected children; neither included in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS program
Allocation concealment (selection bias)	Low risk	Likely to be adequate: treatment masked to investigators Quote: "A randomisation or subject number identified uniquely the vaccine dose to be administered to the subject", and "subjects were administered the vaccine dose with the lowest number available at the study site".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "The study was performed under double-blind with respect to the groups within each study part".
Incomplete outcome data (attrition bias) All outcomes	Low risk	14/192 participants dropped out of the study; balanced between groups with reasons provided.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Unclear risk	No information

RIX Vesikari 2004b-FIN

Study characteristics

Methods	RCT Unbalanced randomization (2:1) **Length of follow-up:** 1 and 2 years of follow-up were 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 gastroenteritis within the previous 7 days.

RIX Vesikari 2004b-FIN *(Continued)*

Interventions	1. RIX4414 (Rotarix): $10^{4.7}$ 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 hour before administration of the study vaccine.
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea: occurrence of rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first rotavirus season following vaccination as detected by RT-PCR in stool samples; occurrence of asymptomatic rotavirus infections during the period starting from 1 month after dose 2 until the end of each rotavirus season following vaccination; G type of the wild rotavirus strain by RT-PCR; measured at 1 year (first report) and 2 years (second report) 2. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 15-day solicited follow-up period after each dose; measured at 15 days after each dose 3. Adverse events requiring discontinuation: occurrence of unsolicited symptoms within 42 days after each dose, according to WHO's classification; measured 42 days after each dose 4. Serious adverse events: no definition; measured at all follow-ups 5. All-cause diarrhoea: gastroenteritis was defined as diarrhoea (≥ 3 looser-than-normal stools within any day) and/or vomiting (≥ 1 episodes of forceful emptying of partially digested stomach contents > 1 hour after feeding within any day); 2 occurrences of gastroenteritis were classified as separate episodes if there were ≥ 5 symptom-free days between them 6. Severe rotavirus diarrhoea: score of < 7 prospectively defined as mild; score of 7 to 10 as moderate; and a score > 11 as severe 7. Rotavirus diarrhoea resulting in hospitalization 8. All-cause death 9. Dropouts **Outcomes to measure immunogenicity** 10. Seroconversion: anti-rotavirus antibody IgA concentration of ≥ 20 units/mL in infants negative for this before the first dose (review included data from 1 month after dose 2)
Immunization status	Infant routine vaccinations (diphtheria tetanus toxoids-pertussis, *H. influenzae* type b, and inactivated poliovirus vaccines) were separated from the study vaccines by at least 2 weeks.
Location	6 centres in Finland Low-mortality country
Notes	**Date:** 21 August 2000 to 11 July 2002 **Source of funding:** GlaxoSmithKline Biologicals **Other:** GSK 444663/004 (rota-004annex) reported a second year extension of the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible infants were randomly assigned (2:1 ratio) to 2 study groups according to a computer-generated randomization list to receive the vaccine or placebo by mouth".

RIX Vesikari 2004b-FIN *(Continued)*

Allocation concealment (selection bias)	Low risk	Likely to be adequate: treatment masked to investigators Quote: "A randomisation or subject number identified uniquely the vaccine dose to be administered to each subject", and "subjects were administered the vaccine dose with the lowest number available at the study site".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "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) All outcomes	Low risk	33/405 participants dropped out of the study; balanced between groups with reasons provided
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	No information

RIX Vesikari 2007a-EU

Study characteristics	
Methods	RCT **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	1. RIX4414 (Rotarix): $10^{6.5}$ 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)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause diarrhoea: gastroenteritis defined as diarrhoea characterized by at least 3 looser-than-normal stools within a day, with or without vomiting; measured 2 weeks after dose 2 until end of 2 years follow-up 2. Rotavirus diarrhoea: trialists deemed a gastroenteritis episode to be caused by rotavirus if a rotavirus strain was identified in a stool sample collected during the episode or within 7 days after res-

RIX Vesikari 2007a-EU *(Continued)*

	olution of symptoms, or before the next episode if fewer than 7 days had fallen between the end of 1 episode and the start of the next, in cases of multiple episodes; measured 2 weeks after dose 2 until end of 2 years follow-up. 3. Severe rotavirus diarrhoea: score < 7 was defined prospectively as mild, score of 7 to 10 as moderate, and a score of ≥ 11 as severe 4. Severe all-cause diarrhoea: as for severe rotavirus diarrhoea 5. Emergency department visit: no definition 6. All-cause hospitalization admission: no definition 7. Serious adverse events: no definition 8. Rotavirus diarrhoea resulting in hospitalization 9. Rotavirus diarrhoea requiring medical attention (defined as "medical personnel contact, advice, or visit; emergency room contact or visit; or admission") 10. Reactogenicity **Outcomes to measure immunogenicity** 11. Seroconversion: appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/mL in participants seronegative for rotavirus before vaccination (review included data from 1 to 2 months after dose 2)
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 *H. influenzae* type b vaccines were co-administered.
Location	98 centres in 6 European countries (Czech Republic, Finland, France, Germany, Italy, and Spain) Low-mortality countries
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "GSK Biologicals provided vaccine supplies that were numbered with a computer-generated randomization list".
Allocation concealment (selection bias)	Low risk	Quote: "randomization was done by a central Internet randomization system. Infants were randomly allocated in a 2/1 ratio two doses of either RIX4414 or placebo".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "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

RIX Vesikari 2007a-EU *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Data were provided only for rotavirus gastroenteritis and for severe gastroenteritis, not for all gastroenteritis episodes.
Other bias	Unclear risk	No information

RIX Vesikari 2011-FIN

Study characteristics	
Methods	RCT **Length of follow-up:** 2 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 to 10 weeks with a birth weight > 2 kg **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*/(Rotarix), 1.5 mL (n = 100) 2. Placebo corresponding to liquid vaccine formulation (n = 25) 3. Lyophilized formulation RIX4414*/(Rotarix), 1 mL (n = 100) 4. Placebo corresponding to lyophilized vaccine formulation (n = 25) * vaccine containing at least 10^6 median $CCID_{50}$ of live attenuated RIX4414 human rotavirus strain **Schedule:** 2 oral doses at month 0 and 1 (minimum time interval between doses: 14 days)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity, occurrence of the symptom within the 15-day solicited follow-up period after each dose (collected from GSK report) 2. Serious adverse events, occurrence throughout study period 3. * Rotavirus diarrhoea, stool samples collected during diarrhoea episodes tested for rotavirus strains 4. * All-cause diarrhoea, up to 1 month post-dose 2 5. Dropouts: up to 2 months after dose 2 (collected from GSK report) 6. All-cause death (collected from GSK report) 7. Adverse events resulting in discontinuation (collected from GSK report) **Outcomes to measure immunogenicity**

RIX Vesikari 2011-FIN *(Continued)*

	8. Seroconversion, antirotavirus IgA antibody concentration > 20 U/mL, 1 month after each dose (collected from GSK report) 9. Rotavirus vaccine virus shedding in stools, reported at peak (day 7 post-dose 1) * Outcome reported as proportion (P) with 95% CI. Events (n) and totals (N) were estimated by using the value when 2 formulae for the standard error (SE) converged.
Immunization status	Routine childhood vaccinations were allowed according to local practice, but at least 14 days apart from each dose of study vaccine.
Location	5 centres in Finland Low-mortality country
Notes	Study known as *RV1 GSK[048] 2007-EU* in previously published versions of this review **Date:** August to November 2005 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** the immunogenicity, reactogenicity and safety of the Rotarix liquid formulation were compared with lyophilized formulation and placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated Quote: "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)	Low risk	Likely to be adequate: treatment masked to investigators Quote: "a unique randomization number identified the vials to be administered to the same subject" and "subjects were administered the vaccine dose with the lowest treatment number available at the study centre".
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel were blinded as far as technically possible. Quote: "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) All outcomes	Low risk	Attrition balanced across study groups with reasons for dropout/exclusion reported
Selective reporting (reporting bias)	Low risk	All pre-published outcomes reported
Other bias	Low risk	No apparent other bias

RIX Ward 2006-USA

Study characteristics

Methods	RCT

RIX Ward 2006-USA *(Continued)*

	Length of follow-up: 7 days following each vaccination; 3 to 5 weeks after second vaccination **Adverse event data collection methods:** unclear
Participants	**Number:** 117 enrolled; 111 evaluable **Age range:** 3 to 6 months (beginning); 3 to 6 months (end) **Inclusion criteria:** not specified **Exclusion criteria:** not specified
Interventions	1. RIX4414 (Rotarix) 1.1. 1 x 10^5 dose; 41 participants (randomized) 1.2. 1 x 10^6 dose; 39 participants (randomized) 2. Placebo: 37 participants **Schedule:** 2 doses given at a 6- to 10-week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose *Although mentioned in the methods, no results were presented. **Outcomes to measure immunogenicity** 2. Vaccine take: faecal shedding of rotavirus antigen (review included data from after either dose 1 or 2) 3. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4 fold) (review included data from after either dose 1 or 2)
Immunization status	Not specified
Location	Cincinnati and Baltimore, USA Low-mortality country
Notes	**Date:** July to December 1996 **Source of funding:** "Avant Immunotherapeutics, to which the 89-12 vaccine candidate was licensed and which sublicensed its product to GlaxoSmithKline (which developed Rotarix from 89-12)" 89-12 was the precursor to Rotarix.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	Quote: "double-blinded, placebo-controlled study designed"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blinded, placebo-controlled study designed"

RIX Ward 2006-USA *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No impact on intervention effect estimate Quote: "Of the 80 vaccine recipients in this trial, 2 had evidence of natural rotavirus infection before administration of the first dose, determined on the basis of rotavirus IgA in their serum. These, along with the 3 who received only 1 dose of vaccine, were eliminated from further analyses".
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

RIX Zaman 2009-BGD

Study characteristics	
Methods	RCT **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	1. RIX4414 (Rotarix) 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
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 8-day (day 0 to 7) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 31 days (day 0 to 30) after each dose, according to MedDRA classification; measured up to 31 days after vaccine/placebo 2. Serious adverse events: occurrence throughout entire study period (up to 105 days after vaccine/placebo)

RIX Zaman 2009-BGD *(Continued)*

	3. Dropouts: measured up to 105 days after vaccine/placebo 4. Rotavirus diarrhoea: presence of rotavirus in gastroenteritis episode stools collected from dose 1 of vaccine/placebo up to 2 months after dose 2; measured up to 105 days after vaccine/placebo 5. All-cause death 6. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 7. Viral shedding: % participants with rotavirus antigen in stool samples collected at predetermined time points (ATP cohort for immunogenicity, stool analysis subset) (review included data from combined time points) 8. Seroconversion: appearance of anti-rotavirus immunoglobulin A antibody concentration ≥ 20 U/mL in participants who were negative for rotavirus before vaccination (review included data from 1 month after dose 2)
Immunization status	All children in the study received the standard EPI vaccines starting at 6 weeks of age, including oral polio vaccine for 1 Rotarix vaccine arm and 1 placebo arm
Location	Single site in urban Dhaka at Mirpur, Bangladesh High-mortality country
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, using a SAS program
Allocation concealment (selection bias)	Low risk	Likely to be adequate: treatment masked to investigators Quote: "A treatment number identified uniquely the vaccine doses to be administered to the same subject", and "subjects were administered the study vaccine dose (HRV vaccine or placebo) with the lowest number available at the study site".
Blinding (performance bias and detection bias) All outcomes	Low risk	Parent/guardian and study personnel were not aware of the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data imputed appropriately
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Unclear risk	No information

RIX Zaman 2017-BGD

Study characteristics	
Methods	Cluster-RCT, open-label, cluster-randomized (by village), parallel-group field trial with an observed-only control group **Length of follow-up:** 2 years **Adverse event data collection methods:** (not reported if active of passive)"Serious adverse events among infants vaccinated with HRV were assessed by the principal investigator or trained study physicians and followed to resolution".
Participants	**Number:** 12,318 enrolled; 11,004 evaluable **Age range:** 6 to 20 weeks **Inclusion criteria:** 6 to 20 weeks of age, having primary residence at the time of DTP dose 1 receipt in a village selected for introduction of HRV, and having a parent or guardian provide written informed consent **Exclusion criteria:** history of intussusception, hypersensitivity to the active substance or any component in the vaccine, uncorrected congenital malformation of the gastrointestinal tract, or known or suspected immunodeficiency. Infants with an acute febrile illness were temporarily excluded from HRV vaccination only if that illness was severe enough to warrant postponement of other EPI vaccinations. Infants with current diarrhoea or vomiting or both were not excluded unless the illness met the aforementioned temporary exclusion criterion.
Interventions	1. Rotarix: 1 mL dose of HRV (GSK Biologicals, Rixensart, Belgium) (n = 71 villages with 6527 age-eligible infants) 2. Non-placebo controlled (observed only controls) (n = 71 villages with 5791 age-eligible infants) **Schedule:** at 6 and 10 weeks of age
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Severe rotavirus diarrhoea 2. Serious adverse events:intussuseption 3. Rotavirus diarrhea of any severity
Immunization status	HRV was scheduled to be given along with other standard infant vaccines including OPV at the DTP dose 1 and 2 immunization visits, recommended in Bangladesh to occur at 6 and 10 weeks of age.
Location	142 study sites (cluster-randomized villages), Bangladesh High-mortality country
Notes	**Date:** September 2008 to March 2011 **Source of funding:** GAVI and PATH **Study rationale:** The primary objective of the trial was to estimate the overall effectiveness of an HRV vaccination programme in reducing the risk of presenting with acute rotavirus diarrhoea to a treatment facility among all children who had been age-eligible for vaccination with HRV during the vaccination programme.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

RIX Zaman 2017-BGD *(Continued)*

Random sequence generation (selection bias)	Low risk	Villages were randomized in a 1:1 ratio for introduction of HRV or not. Prior to study initiation, PATH computer generated the allocation sequences using block randomization with block sizes of 12.
Allocation concealment (selection bias)	Unclear risk	The generated allocation sequences were securely transferred to the principal investigator, who distributed the sequences to the field supervisors who oversaw HRV vaccinations.
Blinding (performance bias and detection bias) All outcomes	High risk	The study was conducted open-label without masking, and field staff conducting the vaccinations were unblinded. Medical staff collecting clinical data on diarrhoeal presentations and laboratory personnel conducting assays on stools were not informed of previous HRV receipt of participants.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcome data available for 11,004/12,318 enrolled participants
Selective reporting (reporting bias)	High risk	Online registration of trial (NCT00737503) indicates all-cause diarrhoea as an outcome but results were not reported for this outcome in the study report.
Other bias	Unclear risk	Cluster-randomized trial

SIIL Isanaka 2017-NER

Study characteristics	
Methods	Double-blind, placebo-controlled, randomized trial **Length of follow-up:** 24 months **Adverse event data collection methods**: Active (scheduled weekly home visits) and passive (facility- and home-based surveillance)
Participants	**Number:** 4092 enrolled, 4086 anaysed (ITT population), 3508 analysed (per-protocol population) **Inclusion criteria:** Healthy infants, 6 to 8 weeks old **Exclusion criteria:** Unable to swallow or history of vomiting within 24 hours, known history of congenital abdominal disorders, intussusception, or abdominal surgery, receipt of intramuscular, oral, or intravenous corticosteroid treatment within 2 weeks, receipt or planned administration during the study period of a blood transfusion or blood products, including immunoglobulins, non-resident in Madarounfa Health District within 15 km of central health facility, not intending to remain in the study area for 2 years, any other condition in which, in the judgement of the investigator, would interfere with or serves as a contraindication to protocol adherence or the parent/guardian's ability to give informed consent
Interventions	1. 3 doses bovine-human reassortant pentavalent rotavirus vaccine (BRV-PV) 2. 3 doses placebo *virus titres of human strains G1, G2, G3, G4, and G9, > 5.6 $\log_{10}$ fluorescent focus units per serotype per dose **Schedule:** 3 doses given at a 4-week interval at 6, 10, and 14 weeks of age
Outcomes	1. Severe rotavirus diarrhoea 2. Severe all-cause diarrhoea

SIIL Isanaka 2017-NER *(Continued)*

	3. All-cause death 4. Serious adverse events 5. Intussusception 6. Rotavirus diarrhoea of any severity 7. All-cause diarrhoea of any severity 8. Reactogenicity: fever, diarrhoea, vomiting 9. Dropouts before the end of the trial
Immunization status	Vaccines that were routinely administered according to the guidelines of the EPI were concomitantly administered with the vaccine or placebo.
Location	Niger (single centre) High-mortality country
Notes	**Date:** August 2014 to November 2015 **Source of funding:** Médecins sans Frontières and the Kavli Foundation; vaccine, buffer, and placebo donated by the Serum Institute of India **Study rationale:** As part of an effort to identify rotavirus vaccines for use in resource-constrained settings, the efficacy and safety of BRV-PV against severe rotavirus gastroenteritis among healthy infants in Niger were assessed..

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Unique assignment numbers were prepared with the use of a computer-generated random-number list with nondisclosed permuted blocks of random sizes (DiagnoSearch Life Sciences)."
Allocation concealment (selection bias)	Low risk	Quote: "Vaccine and placebo packages were labeled with assignment numbers with identical presentation. All the practitioners and participants were unaware of the treatment assignments."
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, carers, investigators, Data Safety Monitoring Board, and statistician were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All or nearly all enrolled participants were included in safety analyses (low risk of bias). 86% of enrolled participants were included in efficacy analyses (unclear risk of bias). Reasons for missing data were lost to follow-up (n = 37), withdrew consent (30), moved from study area (17), received another rotavirus vaccine (2). Missing data were balanced between trial arms.
Selective reporting (reporting bias)	Low risk	All outcomes listed in the online trial record (NCT02145000) were fully reported in the publication.
Other bias	Low risk	No other sources of bias were detected.

SIIL Kulkarni 2017-IND

Study characteristics	
Methods	Double-blind, placebo-controlled, randomized trial **Length of follow-up:** until the children were 2 years of age **Adverse event data collection methods**: Active (home visits for reactogenicity cohort) and passive (diary cards for reactogenicity cohort and ongoing surveillance for all)
Participants	**Number:** 7505 enrolled, 7500 analysed, 1009 analysed for reactogenicity (reactogenicity cohort) **Inclusion criteria:** Healthy infants, 6 to 8 weeks old **Exclusion criteria:** Significant malnutrition, systemic disorder, congenital abdominal disorder, history of persistent diarrhoea, intussusception, abdominal surgery, suspected immune compromised status, allergy to any components of the study vaccines, known major congenital defect. Infants with ongoing diarrhoea or vomiting, fever, or any acute disease were temporarily excluded.
Interventions	1. 3 doses bovine-human reassortant pentavalent rotavirus vaccine (BRV-PV)* 2. 3 doses placebo *virus titres of human strains G1, G2, G3, G4, and G9: 5.934-6.241 $\log_{10}$ FFU/vial **Schedule:** 3 doses given at a 4-week interval at 6, 10, and 14 weeks of age
Outcomes	1. Severe rotavirus diarrhoea 2. Severe all-cause diarrhoea 3. All-cause death 4. Serious adverse events 5. Intussusception 6. Rotavirus diarrhoea of any severity 7. Rotavirus diarrhoea requiring hospitalization 8. Reactogenicity: fever, diarrhoea, vomiting 9. Adverse events requiring discontinuation 10. Dropouts before the end of the trial
Immunization status	The routine DTP-Hepatitis B-Hib and oral polio vaccines were administered concomitantly.
Location	India (six centres) **Setting:** High-mortality country
Notes	**Date:** May 2014 to February 2017 **Source of funding:** PATH Vaccine Solutions, USA and Serum Institute of India Ltd. **Study rationale:** To assess the clinical efficacy of the BRV-PV vaccine in preventing severe rotavirus gastroenteritis and expand on the safety observations made in earlier trials

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

SIIL Kulkarni 2017-IND *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "computer-generated allocation schedule"
Allocation concealment (selection bias)	Low risk	Quote: "assignments were provided to the sites by a validated interactive web response system".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "All the study vaccine containers looked identical with unique vial numbers printed on them to maintain blinding." Comment: Participants, carers, and study personnel/investigators were probably blinded. No details on blinding of outcome assessment were reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions from safety outcomes and ITT analyses (low risk of bias). Less that 15% of the participants were included for reactogenicity outcomes (high risk of bias).
Selective reporting (reporting bias)	Low risk	All outcomes listed in the online trial record (NCT02133690) were fully reported in the publication.
Other bias	Low risk	No other sources of bias were detected.

SIIL Zade 2014-INDa

Study characteristics	
Methods	Phase I, randomized, double-blind, placebo-controlled trial **Length of follow-up**: 28 days **Adverse event data collection methods**: Not reported
Participants	**Number**: 36 (18 infants and 18 toddlers) enrolled*; not reported how many were analysed *18 adults were also enrolled but not included in this review. **Inclusion criteria**: Healthy infants, 8-10 weeks of age at the time of vaccination, born with more than 37 week gestation, birth weight 2500 g or above; healthy toddlers, aged between 2-5 years, normal weight for age **Exclusion criteria**: Prior receipt of any rotavirus vaccine; fever at the time of immunization; history of diarrhoea or blood in stool or abnormal stool pattern in past one week; a known sensitivity or allergy to any components of the study medication; history or presence of asthma, urticaria or other allergic reaction; history of chronic gastrointestinal disease, intussusception, gastrointestinal malformation or abdominal surgery; presence of any significant systemic disorder (cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, neurological, cancer or autoimmune disease) which would endanger the subjects' health or is likely to result in non-conformance to the protocol; major congenital or genetic defect; has received immunosuppressant for more than 14 days or other immune-modifying drugs; has any confirmed or suspected immunosuppressive or immunodeficiency condition; household contact with an immunosuppressed individual or pregnant woman; has received any immunoglobulin therapy or blood products prior to start of study; use of any investigational or non-registered drug other than the study vaccine(s) within 30 days preceding the first dose of the study vaccine or placebo, or planned use during the study period; subjects participating in any other clinical trial; participation in a drug research study within past 3 months; subject is not suitable for inclusion in the study in the opinion of the investigator; investigator site personnel directly affiliated with this study and their immediate families; subject has received any other vaccine within the past 7 days preceding the study vaccine administration
Interventions	1. One dose bovine-human reassortant pentavalent rotavirus vaccine* (BRV-PV) 2. One dose placebo

SIIL Zade 2014-INDa *(Continued)*

	*10^6FFU/serotype (G1, G2, G3, G4 and G9) **Schedule**: Single dose
Outcomes	1. Serious adverse events (reported narratively in results text; not in analysis)
Immunization status	Not reported
Location	India (single site) High-mortality country
Notes	**Date**: from October 2009 (end not reported) **Source of funding**: Serum Institute of India **Study rationale**: To assess the safety of a single oral dose of BRV-PV sequentially in healthy adults, toddlers and infants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Permuted block randomization, fixed"
Allocation concealment (selection bias)	Low risk	Quote: "Pre-numbered or coded identical Containers"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Participant, Investigator and Outcome Assessor Blinded"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants that were analysed was not reported.
Selective reporting (reporting bias)	Unclear risk	Solicited adverse events listed as primary outcome in the trial registry (CTRI/2009/091/000821) were not fully reported.
Other bias	Unclear risk	Absence of other sources of bias could not be confirmed due to the very brief report.

SIIL Zade 2014-INDb

Study characteristics	
Methods	Phase II, randomized, double-blind, placebo-controlled trial **Length of follow-up**: 28 days **Adverse event data collection methods**: Not reported
Participants	**Number**: 60 enrolled; 57 analysed **Inclusion criteria**: Healthy infants, 8-10 weeks of age at the time of vaccination, born with more than 37 week gestation, birth weight 2500 g or above

SIIL Zade 2014-INDb *(Continued)*

	Exclusion criteria: Prior receipt of any rotavirus vaccine; fever at the time of immunization; history of diarrhoea or blood in stool or abnormal stool pattern in past one week; a known sensitivity or allergy to any components of the study medication; history or presence of asthma, urticaria or other allergic reaction; history of chronic gastrointestinal disease, intussusception, gastrointestinal malformation or abdominal surgery; presence of any significant systemic disorder (cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, neurological, cancer or autoimmune disease) which would endanger the subjects' health or is likely to result in non-conformance to the protocol; major congenital or genetic defect; has received immunosuppressant for more than 14 days or other immune-modifying drugs; has any confirmed or suspected immunosuppressive or immunodeficiency condition; household contact with an immunosuppressed individual or pregnant woman; has received any immunoglobulin therapy or blood products prior to start of study; use of any investigational or non-registered drug other than the study vaccine(s) within 30 days preceding the first dose of the study vaccine or placebo, or planned use during the study period; subjects participating in any other clinical trial; participation in a drug research study within past 3 months; subject is not suitable for inclusion in the study in the opinion of the investigator; investigator site personnel directly affiliated with this study and their immediate families; subject has received any other vaccine within the past 7 days preceding the study vaccine administration
Interventions	1. 3 doses bovine-human reassortant pentavalent rotavirus vaccine* (BRV-PV) 2. 3 doses placebo *$10^{5.2}$FFU/serotype (G1, G2, G3, G4 and G9) **Schedule**: 3 doses with at least four weeks interval between doses
Outcomes	1. Reactogenicity: fever, diarrhoea, vomiting 2. Serious adverse events (reported narratively in results text; not in analysis)
Immunization status	Not reported
Location	India (single site) High-mortality country
Notes	**Date**: Not reported **Source of funding**: Serum Institute of India **Study rationale**: To assess safety and tolerability

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Permuted block randomization, fixed"
Allocation concealment (selection bias)	Low risk	Quote: "Pre-numbered or coded identical Containers"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Participant, Investigator and Outcome Assessor Blinded"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10% (3/30) of partcipants in the intervention group were not analysed; reasons for missing data were not reported.
Selective reporting (reporting bias)	Low risk	All outcomes listed in the online trial record (CTRI/2009/091/000821) were fully reported in the publication.

SIIL Zade 2014-INDb *(Continued)*

Other bias	Unclear risk	Absence of other sources of bias could not be confirmed due to the very brief report.

SIIL Zade 2014-INDc

Study characteristics	
Methods	Phase II, randomized, double-blind, placebo-controlled trial **Length of follow-up:** 28 days **Adverse event data collection methods**: Not reported
Participants	**Number**: 60 enrolled and analysed **Inclusion criteria**: Healthy infants, 8-10 weeks of age at the time of vaccination, born with more than 37 week gestation, birth weight 2500 g or above **Exclusion criteria**: Subjects participating in any other clinical trial; prior receipt of any rotavirus vaccine; fever at time of immunization; history of diarrhoea or blood in stool or abnormal stool pattern in past one week; a known sensitivity or allergy to any components of the study medication; history of chronic gastrointestinal disease, intussusception, gastrointestinal malformation or abdominal surgery; presence of any significant systemic disorder (cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, neurological, cancer or autoimmune disease) which would endanger the subject's health or is likely to result in non-conformance to the protocol; major congenital or genetic defect; has received immunosuppressant for more than 14 days or other immune-modifying drugs prior to the first vaccine dose; any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection based on medical history and physical examination; household contact with an immunosuppressed individual or pregnant woman; has received any immunoglobulin therapy and/or blood products since birth or planned administration during the study period; subject is not suitable for inclusion in the study in the opinion of the investigator; investigator site personnel directly affiliated with this study and their immediate families; use of any investigational or non-registered drug other than the study vaccine(s) within 30 days preceding the first dose of the study vaccine or placebo, or planned use during the study period
Interventions	1. 3 doses bovine-human reassortant pentavalent rotavirus vaccine* (BRV-PV) 2. 3 doses placebo *$10^{5.6}$FFU/serotype (G1, G2, G3, G4 and G9) **Schedule**: 3 doses with at least four weeks interval between doses
Outcomes	1. Reactogenicity: fever, diarrhoea, vomiting 2. Serious adverse events
Immunization status	Other childhood vaccines such as DTP, OPV, Hepatitis B vaccine, *Haemophilus influenzae* type b, or BCG with at least 7 days separation from the first and subsequent dose of the study vaccine
Location	India (two sites) High-mortality country
Notes	**Date**: from Januaty 2011 (end not reported) **Source of funding**: Serum Institute of India **Study rationale**: To assess safety, tolerability, immunogenicity, and viral shedding

SIIL Zade 2014-INDc *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Permuted block randomization, fixed"
Allocation concealment (selection bias)	Low risk	Quote: "Pre-numbered or coded identical Containers"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Participant, Investigator and Outcome Assessor Blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were analysed.
Selective reporting (reporting bias)	Low risk	All outcomes listed in the online trial record (CTRI/2010/091/003064) were fully reported in the publication.
Other bias	Unclear risk	Absence of other sources of bias could not be confirmed due to the very brief report.

TEQ Armah 2010-AF

Study characteristics	
Methods	RCT **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

TEQ Armah 2010-AF *(Continued)*

Interventions	1. WC3 (RotaTeq): 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
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events (including intussusception) 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both, and (2) rotavirus detected by enzyme immunoassay (EIA) in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured at up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea – severe 7. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose (review included data from for the end of follow-up) *Data on fever and vomiting were provided only in figure 2 and data could not be extracted reliably. **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4-fold) (review included data from after dose 2)
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) High-mortality countries
Notes	This trial was conducted in Ghana, Kenya and Mali; data reported separately by country can be found under TEQ Armah 2010-GHA; TEQ Armah 2010-KEN and TEQ Armah 2010-MLI. **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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six".

TEQ Armah 2010-AF *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "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) All outcomes	Low risk	Participants and staff: Quote: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial". Researchers: Quote: "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) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	No apparent other bias

TEQ Armah 2010-GHA

Study characteristics	
Methods	RCT **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".
Participants	**Number:** 2200 randomized **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 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
Interventions	1. WC3 (RotaTeq): 2 mL (every dose had an estimated potency of 10^7 infectious units per reassortant rotavirus); 3 doses given 4 weeks apart; 1098 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 1102 participants (randomized) **Schedule:** 3 doses given at a 4-week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events (including intussusception)

TEQ Armah 2010-GHA *(Continued)*

	2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured at up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea – severe 7. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose (review included data from for the end of follow-up) *Data on fever and vomiting were provided only in figure 2 and data could not be extracted reliably. **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4-fold) (review included data from after dose 2)
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 High-mortality country
Notes	This trial was conducted in Ghana, Kenya and Mali; this part presents data for the Ghana cohort. Data reported separately for the other countries can be found under TEQ Armah 2010-KEN and TEQ Armah 2010-MLI; data reported for all countries under TEQ Armah 2010-AF. **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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six".
Allocation concealment (selection bias)	Low risk	Quote: "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) All outcomes	Low risk	Participants and staff: Quote: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial". Researchers:

TEQ Armah 2010-GHA *(Continued)*

		Quote: "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) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	No apparent other bias

TEQ Armah 2010-KEN

Study characteristics	
Methods	RCT **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:** 1322 enrolled; 1308 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	1. WC3 (RotaTeq): 2 mL (every dose had an estimated potency of 10^7 infectious units per reassortant rotavirus); 3 doses given 4 weeks apart; 656 participants (received at least one dose) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 652 participants (received at least one dose) **Schedule:** 3 doses given at a 4-week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events (including intussusception) 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful

TEQ Armah 2010-KEN *(Continued)*

	vomiting, or both, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured at up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea – severe 7. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose (review included data from for the end of follow-up) *Data on fever and vomiting were provided only in figure 2 and data could not be extracted reliably. **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4-fold) (review included data from after dose 2)
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 Karemo division, Siaya district, Kenya High-mortality country
Notes	This trial was conducted in Ghana, Kenya and Mali; this part presents data for the Kenya cohort. Data reported separately for the other countries can be found under TEQ Armah 2010-GHA and TEQ Armah 2010-MLI, and for all countries under TEQ Armah 2010-AF. **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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six".
Allocation concealment (selection bias)	Low risk	Quote: "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) All outcomes	Low risk	Participants and staff: Quote: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial". Researchers: Quote: "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

TEQ Armah 2010-KEN *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	No apparent other bias

TEQ Armah 2010-MLI

Study characteristics	
Methods	RCT **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".
Participants	**Number:** 2011 enrolled; 1960 randomized and 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 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
Interventions	1. WC3 (RotaTeq): 2 mL (every dose had an estimated potency of 10^7 infectious units per reassortant rotavirus); 3 doses given 4 weeks apart; 979 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 981 participants (randomized) **Schedule:** 3 doses given at a 4-week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events (including intussusception) 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured at up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea – severe

TEQ Armah 2010-MLI *(Continued)*

	7. Reactogenicity *: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose (review included data from for the end of follow-up) * Data on fever and vomiting were provided only in figure 2 and data could not be extracted reliably. **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4-fold) (review included data from after dose 2)
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 urban area of Bamako, Mali High-mortality country
Notes	This trial was conducted in Ghana, Kenya and Mali; this part presents data for the Mali cohort. **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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six".
Allocation concealment (selection bias)	Low risk	Quote: "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) All outcomes	Low risk	Participants and staff: Quote: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial". Researchers: Quote: "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) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	No apparent other bias

TEQ Block 2007-EU/USA

Study characteristics

TEQ Block 2007-EU/USA *(Continued)*

Methods	RCT **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	1. WC3 (RotaTeq): 1.1 x 10^7 PFU; 651 participants (randomized) 2. Placebo: 661 participants (randomized) **Schedule:** 3 doses given 4 to 10 weeks apart
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events: potential cases of intussusception were adjudicated by an independent blinded committee; all study personnel remained blinded to the treatment arm and adjudication results of the potential intussusception cases; data on cases of intussusception, deaths, or other serious adverse events determined to be vaccine-related by the investigator were collected throughout the trial; measured up to 42 days, and up to 1 year (for vaccine-related serious adverse events) 2. Reactogenicity: no definition; measured up to 42 days 3. Dropouts: no definition: measured up to 1 year 4. Rotavirus diarrhoea: case of rotavirus gastroenteritis defined as meeting both of the following criteria: (a) > 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both; and (b) rotavirus antigen detection by EIA in the stool sample. Primary analysis of efficacy included only cases caused by naturally-occurring rotavirus of serotypes G1, G2, G3, or G4 as confirmed by RT-PCR occurring at least 14 days after the third dose 5. Severe rotavirus diarrhoea: each episode graded on a 24-point scale, where a score < 8 designated as mild, > 8 as moderate-and-severe, and > 16 as a severe disease 6. All-cause death 7. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity**

TEQ Block 2007-EU/USA *(Continued)*

	8. Seroconversion: pre-vaccination and post-vaccination sera analysed for serotype-specific rotavirus neutralizing antibody and for serum anti-rotavirus immunoglobulin A (IgA) (review included data from after dose 3)
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 Low-mortality countries
Notes	**Date:** 24 September 2002 (first participant in) to 11 February 2004 **Source of funding:** Merck & Co., Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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) All outcomes	Low risk	Quote:"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) All outcomes	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

TEQ Ciarlet 2009-EU

Study characteristics

Methods	RCT **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)

TEQ Ciarlet 2009-EU *(Continued)*

	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, DTPa, DTP, *H. 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 RotaTeq 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	1. WC3 (RotaTeq) plus Infanrix hexa: RotaTeq (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 *H. influenzae* type b vaccine and is a white pellet in a separate glass vial; both parts mixed together before being injected intramuscularly
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: in both groups, at each study visit, parents/legal guardians received Vaccination Report Cards (VRCs) which they completed for 7 days with information on fever, diarrhoea, and vomiting starting from the day of office visit and returned completed VRCs to the study site at the next visit. 2. Serious adverse events: parents/legal guardians of all participants were contacted by telephone or home visit on approximately day 14 after each office visit in either group for safety follow-up and asked about all serious adverse experiences; measured up to 42 days 3. All-cause death 4. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** None specific to review
Immunization status	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, polio virus, and *H. influenzae* type b co-administered
Location	26 study sites in Austria, Belgium, and Germany Low-mortality countries
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 were provided.

Risk of bias

Bias	Authors' judgement	Support for judgement

TEQ Ciarlet 2009-EU *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomized 1:1 to receive hexavalent vaccine concomitantly with either RotaTeq or placebo (Merck 2012)
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants, investigators, adults, and parents/guardians of children were blinded throughout trial (Merck 2012).
Blinding (performance bias and detection bias) All outcomes	Low risk	RotaTeq was visibly indistinguishable from placebo; investigators, parents/guardians and study personnel (internal and external) were blinded throughout trial (Merck 2012).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In both treatment groups (RotaTeq + Hexavalent and Placebo + Hexavalent), ~84% of the infants reported 1 or more adverse events within 14 days after vaccination. One subject discontinued in the concomitant-use group because of abdominal pain (considered non-serious)" (Merck 2012).
Selective reporting (reporting bias)	High risk	Not all prespecified outcomes reported
Other bias	Unclear risk	No details

TEQ Clark 2003-USA

Study characteristics	
Methods	RCT **Length of follow-up:** up to 1 year **Adverse event data collection methods:** parents/guardians recorded temperatures 4 to 6 hours 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 behavioural or systemic adverse experience on a VRC 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 minutes 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 hour before vaccination
Interventions	1. WC3 (RotaTeq): 10^7 PFU; 581 participants (randomized) 2. Placebo: 150 participants (randomized) **Schedule:** 3 doses given 42 to 56 days apart
Outcomes	**Clinical outcome measures (safety and efficacy)**

TEQ Clark 2003-USA *(Continued)*

	1. Reactogenicity: parents/guardians recorded temperatures 4 to 6 hours after each dose and then daily thereafter for 7 days and the number of episodes of vomiting and diarrhoea daily for 7 days; fever defined as 38.1 °C (rectal) or 37.5 °C (oral, otic, or axillary); measured up to 42 days after vaccine/placebo 2. Rotavirus diarrhoea: case of rotavirus gastroenteritis defined as ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both, occurring at least 14 days after the third dose of vaccine/placebo and detection by ELISA of wild-type G1 or G2 rotavirus or both in a stool specimen collected within 14 days of symptom onset; measured up to 1 year 3. Severe rotavirus diarrhoea: clinical scoring system used to assess severity of illness for each episode of rotavirus acute gastroenteritis; measured up to 1 year 4. Serious adverse events: defined as: death; life-threatening events; experiences that resulted in hospitalization, persistent disability, or that prolonged a hospitalization; and other important medical events. Data on deaths or any serious adverse experiences judged to be vaccine-related were collected for the duration of the study; measured up to 1 year 5. Intussusception, data from correspondence with Merck (Merck 2012) 6. Dropouts **Outcomes to measure immunogenicity** 7. Viral shedding: at least a 3-fold rise in serum-neutralizing antibody to total stool IgA (review included data from after dose 3) 8. Seroconversion: at least a 3-fold rise in serum-neutralizing antibody to serum IgA (review included data from after dose 3)
Immunization status	Children that had recently received oral polio vaccine were excluded from the study.
Location	19 centres in the USA Low-mortality country
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details Quote: "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) All outcomes	Low risk	Participants and key personnel: Quote: "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

TEQ Clark 2003-USA *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Not all prespecified outcomes reported. Poor reporting of efficacy data. Quote: "Because there were relatively few confirmed cases of RV [rotavirus] caused by serotypes G1 and G2, the evidence is insufficient to declare that the efficacy of any buffered formulation is > 0.0%".
Other bias	Unclear risk	Not enough detail to make a judgement

TEQ Clark 2004-USA

Study characteristics	
Methods	RCT **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 were also 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	1. WC3 (RotaTeq): 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)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea: case of rotavirus disease in a study participant defined as ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both, occurring at least 14 days after the third dose of vaccine/placebo and identification of rotavirus in a stool specimen obtained within 14 days of symptom onset; measured up to 1 year 2. Severe rotavirus diarrhoea: based on a clinical scoring system for evaluating the severity of an episode of infant acute gastroenteritis (0 to 24 points) they consider severe above 16 points; measured up to 1 year 3. Dropouts: measured up to 1 year 4. Serious adverse events: serious adverse experiences included death, life-threatening events, and experiences that resulted in hospitalization, persistent disability, or that prolonged a hospitalization; deaths or any serious adverse experiences judged to be vaccine-related were recorded for the duration of the study; measured up to 1 year, including intussusception (data from correspondence with Merck, Merck 2012).

TEQ Clark 2004-USA *(Continued)*

	5. Reactogenicity: all participants were followed for clinical adverse experiences for 14 days after each vaccination. 6. Adverse events requiring discontinuation; measured up to 1 year **Outcomes to measure immunogenicity** 7. Viral shedding: stools were collected to evaluate vaccine strain shedding among subsets of infants at different time periods after each dose (review included data from after dose 3). 8. Seroconversion: pre-vaccination and post-vaccination sera assayed for anti-rotavirus immunoglobulin A (IgA) and anti-rotavirus IgG (units/mL, based on pooled human serum standards); ≥ 3-fold rise in titre from baseline to after dose 3 (review included data from after dose 3)
Immunization status	Receipt of any other vaccines within 14 days was not allowed.
Location	10 study sites in the USA Low-mortality country
Notes	**Date:** August 1993 to June 1994 **Source of funding:** Merck & Co. Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Infants who met all eligibility criteria were randomly assigned in a 1:1 ratio". No further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The vials of vaccine and placebo were visibly indistinguishable". Quote: "The placebo was identical to the vaccine except that it did not contain the rotavirus reassortants". Investigators, study personnel (internal and external), and parents/guardians were blinded throughout the trial (Merck 2012).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	High risk	≥ 1 outcome of interest reported incompletely Quote: "Only wild-type (i.e. non-vaccine-related) rotavirus cases were considered for the primary case definition".
Other bias	Unclear risk	Not enough detail to make a judgement

TEQ Dhingra 2014-IND

Study characteristics

Methods	RCT **Length of follow-up:** 28 days after 3rd dose

TEQ Dhingra 2014-IND *(Continued)*

	Adverse event data collection methods: Active and passive: "participants were observed for 30 min post-vaccination for immediate adverse events at the study site. Subsequently, the subject's parents/guardians were given a thermometer, a Symptom Diary (SD) covering days 0–6 and a second SD covering days 7–27 for safety follow-up following each of the three doses. They were instructed to observe and record their child's axillary temperature twice daily as well as any AEs up to 7 days after each dose in the first SD, and from day 7 to day 27 in the second SD. Parents/guardians were instructed to bring the study infants to the study clinic on day 7 and day 28 after each administration of the BRV-TV vaccine/RotaTeq/placebo as an outpatient and whenever any symptoms developed. The diary card contained list of solicited events and blank spaces to capture any unsolicited events".
Participants	**Number:** 100 enrolled; 100 evaluated **Age range:** 6-8 weeks of age at time of enrolment **Inclusion criteria:** Healthy infants, of either sex, 6-8 weeks of age at time of enrolment; born after a gestational period of 36-42 weeks with birth weight > 2 kg **Exclusion criteria:** History of congenital abdominal disorders, intussusception, or abdominal surgery; infants exhibiting signs of severe malnutrition; known or suspected impairment of immunological function in participant or immediate family; developmental delay or neurological disorder; known hypersensitivity to any component of the rotavirus vaccine; fever; history of known rotavirus disease, chronic diarrhoea, or failure to thrive; any conditions which, in the opinion of the investigator, might interfere with the evaluation of the study objectives
Interventions	1. RotaTeq (2.0 mL) 2. BRV-TV (2.0 mL), antigen concentration (105.0 FFU per serotype per dose) 3. BRV-TV (2.0 mL), antigen concentration (105.8 FFU per serotype per dose) 4. BRV-TV (2.0 mL), antigen concentration (106.4 FFU per serotype per dose) 5. Placebo (2.0 mL) **Schedule:** 3 doses of vaccines/comparator/placebo were administered at 6–8, 10–12 and 14–16 weeks of age
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All serious adverse events 2. Reactogenicity: fever, diarrhoea, vomiting 3. Dropouts before the end of the trial **Outcomes to measure immunogenicity** 4. Rotavirus vaccine shedding
Immunization status	Infants concomitantly received a combined diphtheria, tetanus, whole-cell pertussis, hepatitis B and *Haemophilus influenzae* type b pentavalent vaccine and trivalent oral polio vaccine
Location	2 sites, India High-mortality country
Notes	Alongside the infant cohort, the study also included an additional cohort of healthy adult volunteers. **Date:** July 2012 - not reported **Source of funding:** Shantha Biotechnics Limited

TEQ Dhingra 2014-IND *(Continued)*

Study rationale: study was carried out with the long-term aim to produce a locally licensed vaccine which is equally safe and immunogenic as compared to available licensed vaccines.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Likely to be adequate: Quote: "Pre-numbered or coded identical containers"
Blinding (performance bias and detection bias) All outcomes	High risk	Single-blind, participant and outcome assessor-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data presented for all 100 participants
Selective reporting (reporting bias)	Low risk	No indication of selective outcome reporting
Other bias	Low risk	No apparent other bias

TEQ Iwata 2013-JPN

Study characteristics

Methods	RCT **Length of follow-up:** 25 months **Adverse event data collection methods:** any death, vaccine-related serious adverse events and intussusception were collected during the study period; parents/guardians asked to record adverse events on a standardized VRC 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 rotavirus gastroenteritis; infants 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 [RotaTeq], 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 gastroenteritis episodes until the end of the study
Outcomes	1. Efficacy against rotavirus gastroenteritis of any severity, at least 14 days following the 3rd vaccination

TEQ Iwata 2013-JPN *(Continued)*

	2. Efficacy against moderate to severe and severe rotavirus gastroenteritis, at least 14 days following the 3rd vaccination 3. Serious adverse events, including intussusception (data from correspondence with Merck; Merck 2012). 4. Reactogenicity (fever, vomiting, diarrhoea) 5. Dropouts before the end of the trial 6. Adverse events leading to discontinuation of the trial 7. Number of deaths (data from correspondence with Merck; Merck 2012)
Immunization status	No information about other vaccines given
Location	32 sites in Japan Low-mortality country
Notes	**Date:** August 2008 to 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation number was assigned and the subject was randomized to the group receiving RotaTeq or the group receiving placebo in a 1:1 ratio according to the randomization code prepared by a computer at the US Merck Headquarters Office" (Merck 2012).
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated and allocated centrally for participants (Merck 2012).
Blinding (performance bias and detection bias) All outcomes	Low risk	RotaTeq was visibly indistinguishable from placebo; investigators, study personnel (internal and external) and parents/guardians were blinded throughout trial (Merck 2012).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusions balanced across groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	No apparent other bias

TEQ Kim 2008-KOR

Study characteristics

Methods	RCT

TEQ Kim 2008-KOR *(Continued)*

	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	1. WC3 (RotaTeq): 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; 63 participants (randomized)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events: no definition; measured up to 42 days 2. Reactogenicity: no definition; measured up to 14 days 3. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 4. Seroconversion: sero-response serum anti-rotavirus immunoglobulin A (IgA) defined as an increase in antibody titre by a factor of ≥ 3 from baseline (data could not be extracted for review)
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 breast-feeding was not restricted.
Location	8 study centres in South Korea Low-mortality country
Notes	**Date:** 2 August 2005 (first participant 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 were not provided in the reports.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomized 2:1 to receive hexavalent vaccine concomitantly with either RotaTeq or placebo (Merck 2012)

TEQ Kim 2008-KOR *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants; investigators, adults, and parents/guardians of children were blinded throughout trial (Merck 2012).
Blinding (performance bias and detection bias) All outcomes	Low risk	RotaTeq was visibly indistinguishable from placebo; investigators, study personnel (internal and external), and parents/guardians were blinded throughout trial (Merck 2012).
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason related to outcome
Selective reporting (reporting bias)	High risk	Key expected outcome not included
Other bias	Unclear risk	Information not provided

TEQ Lawrence 2012-CHN

Study characteristics	
Methods	RCT **Length of follow-up:** 2 weeks after last dose **Adverse event data collection methods:** not reported
Participants	**Number:** Infant cohort: 48 enrolled and randomized, child cohort: 48 enrolled and randomized **Inclusion criteria:** healthy infants aged 6 to 12 weeks, and healthy children aged 2 to 6 years; there was also a cohort of adults (not reported in this review). **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 RotaTeq (V260) administered orally. The vaccine consists of an oral solution of 5 live human-bovine reassortant rotaviruses (24 infants, 24 children). 2. 2.0 mL matching placebo to RotaTeq administered orally (24 infants, 24 children) **Schedule: infant cohort:** 3 doses of RotaTeq/placebo at 3 separate visits scheduled 28 to 70 days apart. The third dose was administered by 32 weeks of age; **child cohort:** one dose
Outcomes	**Clinical outcome measures** 1. Serious adverse events, up to 14 days post-vaccination, including intussusception (data from correspondence with Merck; Merck 2012) 2. Adverse events requiring discontinuation 3. Dropouts from the trial 4. Number of deaths (data from correspondence with Merck; Merck 2012) 5. Reactogenicity **Outcomes to measure immunogenicity** 6. Vaccine virus shedding in stools, day 3 to day 7 following each of the 3 doses of RotaTeq/placebo

TEQ Lawrence 2012-CHN *(Continued)*

Immunization status	Other live vaccines 14 days before or after study vaccine were not allowed.
Location	China Medium-mortality country
Notes	**Date:** September 2009 to March 2010 **Source of funding:** Merck Sharp & Dohme Corp **Study rationale:** "This study will assess the safety and tolerability of RotaTeq (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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All participants were randomized according to a computer-generated allocation schedule (Merck 2012).
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants; investigators, adults, and parents/guardians of children were blinded throughout trial (Merck 2012).
Blinding (performance bias and detection bias) All outcomes	Low risk	RotaTeq was visibly indistinguishable from placebo; investigators, study personnel (internal and external) and parents/guardians were blinded throughout trial (Merck 2012).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across groups with reasons reported for withdrawal
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	No apparent other bias

TEQ Levin 2017-AF

Study characteristics

Methods	RCT **Length of follow-up:** 6 weeks after last dose **Adverse event data collection methods:** Active: At each visit, data were recorded on adverse events observed by the caretaker and investigator, including signs/symptoms ≥ grade 1 and new clinically significant diagnoses.
Participants	**Number:** 202 enrolled; 202 evaluable **Age range:** infants 2 to < 15 weeks **Inclusion criteria:** Participant was born to an HIV-infected mother; presence or absence of HIV RNA or DNA in the blood of the infant; CD4% documented at screening **Exclusion criteria:** concurrent participation in any study of an investigational drug or vaccine, except for studies for prevention of perinatal HIV transmission; gastrointestinal illness or fever; any condition,

TEQ Levin 2017-AF *(Continued)*

	which would, in the opinion of the site investigator, place the participant at an unacceptable risk of injury or render the participant unable to meet the requirements of the protocol
Interventions	1. RotaTeq, 2 mL solution of live reassortant rotaviruses, containing G1, G2, G3, G4 and P1A which contains a minimum of 2.0 2.8 x 10^6 infectious units (IU) per individual reassortant dose, depending on the serotype, and not greater than 116 x 10^6 IUs per aggregate dose in 62 HIV-uninfected but exposed and 37 HIV-infected participants 2. Placebo in 64 HIV-uninfected but exposed and 39 HIV-infected participants **Schedule:** 3 doses of RotaTeq or placebo at intervals of 4-10 weeks with the third dose administered by 32 weeks of age
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause deaths 2. All-cause serious adverse events 3. Hospitalization 4. Reactogenicity: fever, diarrhoea, vomiting **Outcomes to measure immunogenicity** 4. Rotavirus vaccine shedding (after 3rd dose) 5. Seroconversion
Immunization status	Enrolment was closed in participating countries when Rotarix was added to national vaccine schedules.
Location	Botswana (2 sites), United Republic of Tanzania (1 site), Zambia (1 site) and Zimbabwe (2 sites) High-mortality countries
Notes	**Date:** December 2009-January 2014 **Source of funding:** Merck & Co. Inc. and the International Maternal, Pediatric, and Adolescent AIDS Clinical Trial Network (IMPAACT) through the National Institute of Health **Study rationale:** evaluate the safety and immunogenicity of the rotavirus vaccine RotaTeq, in HIV-infected and uninfected children born to HIV-infected mothers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study reported to be randomized, but no details provided on the randomization process
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo-controlled but no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition; reasons provided

TEQ Levin 2017-AF *(Continued)*

Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Unclear risk	Nine infants were unblinded after their first or second dose when rotavirus vaccine became available at their site. The 4 infants found to be on RotaTeq continued to receive their remaining study doses. Of the 5 infants on placebo, 2 were given the 2 recommended doses of Rotarix, but 3 were too old to receive Rotarix.

TEQ Merck[009] 2005-USA

Study characteristics	
Methods	RCT **Length of follow-up:** up to 42 days after vaccination **Adverse event data collection methods:** not reported
Participants	**Number:** 793 enrolled; 706 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 oral polio vaccine 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	1. WC3 (RotaTeq): 2 mL (10.7 PFU); 3 doses given at 4- to 10-week intervals; 680 participants (randomized) 2. Placebo: 3 doses given at 28- to 70-day intervals; 113 participants (randomized)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: no definition; measured 7 days after vaccination 2. Dropouts: measured up to 42 days 3. Adverse events requiring discontinuations: measured up to 42 days, (data from correspondence with Merck; Merck 2012) 4. Serious adverse events: not defined; measured up to 42 days, including intussusception (data from correspondence with Merck; Merck 2012) 5. Number of deaths (data from correspondence with Merck; Merck 2012) **Outcomes to measure immunogenicity**

TEQ Merck[009] 2005-USA *(Continued)*

	None
Immunization status	Infants were excluded if they had or were to receive oral poliovirus vaccine at any time during the study or in the 42 days before the first dose; concomitant administration of other licensed vaccines and breast-feeding was not reported.
Location	10 centres in USA Low-mortality country
Notes	**Date:** 9 May 2003 to 13 August 2004 **Source of funding:** Merck & Co. Inc. **Study objective:** "Comparison of the Immunogenicity and Safety of Three Consistency Lots of RotaTeq in Healthy Infants"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization to 1 of 4 treatment groups. A randomization scheme of 2:2:2:1, with a blocking factor of 14 was used, and participants received either 1 of 3 lots of RotaTeq or placebo (Merck 2012).
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants; investigators, adults, and parents/guardians of children were blinded throughout trial (Merck 2012).
Blinding (performance bias and detection bias) All outcomes	Low risk	RotaTeq was visibly indistinguishable from placebo; investigators, study personnel (internal and external) and parents/guardians were blinded throughout trial (Merck 2012).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

TEQ Mo 2017-CHN

Study characteristics

Methods	RCT **Length of follow-up:** 2 years **Adverse event data collection methods:** Passive: All adverse events were collected for 30 days following each dose.
Participants	**Number:** 4040 enrolled; 4040 evaluable **Age range:** 6–12 weeks (at start of study) **Inclusion criteria:** Healthy infants at least 6 weeks and up to 12 weeks of age at the time of the first study vaccination

TEQ Mo 2017-CHN *(Continued)*

	Exclusion criteria: History of congenital abdominal disorders, prior rotavirus gastroenteritis, chronic diarrhoea, failure to thrive, or abdominal surgery; history of intussusception; impairment of immunological function; acute disease, severe chronic disease, or chronic disease during the acute period; participation in another interventional study; any condition which, in the opinion of the investigator, may interfere with the evaluation of the study objectives
Interventions	1. RotaTeq, 2 mL (n = 2020 randomized) 1.1 RotaTeq alongside staggered EPI (OPV administered as a 1 g oral solution at age ~2½, 3½, and 4½ months, and DTPa administered as a 0.5 mL intramuscular injection at age ~3½, 4½, and 5½ months) 1.2.RotaTeq with concomitant EPI (OPV administered as a 1 g oral solution at age ~2, 3, and 4 months, and DTPa administered as a 0.5 mL intramuscular injection at age ~3, 4, and 5 months) 2. Placebo (n = 2020 randomized) 2.1 placebo alongside staggered EPI (OPV administered as a 1 g oral solution at age ~2½, 3½, and 4½ months, and DTPa administered as a 0.5 mL intramuscular injection at age ~3½, 4½, and 5½ months) 2.2 placebo with concomitant EPI (OPV administered as a 1 g oral solution at age ~2, 3, and 4 months, and DTPa administered as a 0.5 mL intramuscular injection at age ~3, 4, and 5 months) **Schedule**: RotaTeq or placebo at age 2, 3, and 4 months
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Severe rotavirus diarrhoea 2. All-cause deaths 3. Serious adverse events 4. Intussusception 5. Rotavirus diarrhoea (any severity) 6. Reactogenicity: fever, diarrhoea, vomiting 7. Adverse events due to discontinuation 8. Dropouts from the trial
Immunization status	Routine EPI vaccines (OPV, DTPa) either staggered or concomitantly with RotaTeq or placebo
Location	5 sites, China Medium-mortality country
Notes	**Date:** May 2014-June 2015 **Source of funding:** Merck Sharp & Dohme Corp. **Study rationale:** assess the efficacy, safety, and immunogenicity of a 3 dose regimen of RotaTeq™ (V260) in healthy Chinese infants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study reported to be randomized, but no details provided on the randomization process

TEQ Mo 2017-CHN *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded for vaccine versus placebo, not for staggered versus concomitant
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition and reasons provided
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	No apparent other bias

TEQ Vesikari 2006a-FIN

Study characteristics	
Methods	RCT **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	1. WC3 (RotaTeq) 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 2 arms dealing with different G or P serotypes and compared a single arm to placebo.
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required: (1) ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both; and (2) rotavirus antigen detection by EIA. The primary analysis of efficacy considered episodes as positive only when caused by

TEQ Vesikari 2006a-FIN *(Continued)*

	wild-type rotavirus with a vaccine G serotype (G1, G2, G3, or G4) confirmed by PCR occurring at least 14 days after the third dose of vaccine; measured 1 to 3 years 2. Severe rotavirus diarrhoea: clinical scoring system based on the intensity and duration of symptoms of fever, vomiting, diarrhoea, and behavioural changes was used to rate the severity of gastroenteritis, using a 24-point severity scale where a score of 1 to 8 was designated as mild, > 8 was designated as moderate-and-severe, and > 16 was designated as severe; measured 1 to 3 years 3. Reactogenicity: not defined other than all participants were followed for clinical adverse events for 42 days after each dose of vaccine or placebo; parents/guardians were provided with diary cards to record adverse events. 4. Serious adverse events: not defined; noted that they were to be reported immediately. Parents/legal guardians were contacted by phone approximately 14 days after each dose and asked about serious adverse events. Data on deaths and serious adverse events judged by the investigator to be vaccine-related were collected for the duration of the study (up to 42 days). 5. All-cause death **Outcomes to measure immunogenicity** 6. Seroconversion: prevaccination and post-vaccination sera assayed for rotavirus-specific IgA by ELISA with seroconversion defined as ≥ 3-fold rise in antibody titre from baseline to 2 weeks after dose 3 (review included data from 14 days after dose 3)
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 Low-mortality country
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 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated (Merck 2012)
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants; investigators and parents/guardians were blinded throughout trial (Merck 2012).
Blinding (performance bias and detection bias) All outcomes	Low risk	Sequential identical containers: Quote: "The vials containing either vaccine or placebo were visibly indistinguishable." Participants and key personnel: Quote: "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".

TEQ Vesikari 2006a-FIN *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	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

TEQ Vesikari 2006b-INT

Study characteristics	
Methods	RCT **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 chronological 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	1. WC3 (RotaTeq): 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)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms. Only naturally-occurring "rotavirus AGEs" caused by the composite of the human rotavirus G-serotypes in the vaccine (G1, G2, G3, and G4) occurring through the first rotavirus season that began at least 14 days following the third vaccination were included in the primary analysis; measured up to 2 years follow-up

TEQ Vesikari 2006b-INT *(Continued)*

	2. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 24-point severity scale; scores > 16 were considered to indicate severe disease; measured up to 2 years follow-up 3. Emergency department visit: hospitalizations and emergency department visits for acute gastroenteritis; measured up to 1 year of follow-up 4. All-cause hospital admission: see above; measured up to 1 year of follow-up 5. All-cause mortality: measured up to 1 year of follow-up 6. Dropouts: no definition; measured up to 2 years follow-up 7. Serious adverse events: monitored for at least 42 days after each dose for serious adverse events, including intussusception. All suspected cases of intussusception were reported to an independent, blinded adjudication committee, which included a paediatric surgeon, a paediatric radiologist, and a paediatrician with extensive experience in emergency medicine. The committee adjudicated potential cases of intussusception according to a prespecified case definition that required confirmation of the diagnosis by radiography or at surgery or autopsy; measured up to 1 year of follow-up. Final intussusception results taken from CDC report (CDC 2010) 8. Reactogenicity: not defined; measured up to 43 days after vaccine 9. Adverse events requiring discontinuation: not defined; measured up to 1 year of follow-up 10. Rotavirus diarrhoea resulting in hospitalization **Outcomes to measure immunogenicity** 11. Seroconversion: defined as an increase in the antibody titre by a factor of ≥ 3 from baseline (review included data from 14 days after dose 3)
Immunization status	Administration of other licensed childhood vaccines and breastfeeding were not restricted; for a subset of participants in the USA (U.A. concomitant use cohort), Merck also provided the licensed paediatric vaccines that were administered concomitantly (same day) with RotaTeq or placebo, which included Comvax, Infanrix, Ipol, and Prevnar.
Location	356 primary study sites in Europe, Latin America, USA and Taiwan Low- (Belgium, Finland, Germany, Italy, Sweden, Taiwan, USA), Medium- (Costa Rica, Jamaica, Mexico), and High-mortality (Guatemala) countries
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomized 1:1 to receive either RotaTeq or placebo (Merck 2012)
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants; investigators and parents/guardians were blinded throughout trial (Merck 2012).
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel:

TEQ Vesikari 2006b-INT *(Continued)*

		Quote: "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) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Unclear risk	Difficult to judge, as some important information about randomization/allocation concealment were not provided

TEQ Zaman 2010-AS

Study characteristics	
Methods	RCT **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:** 2119 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	1. WC3 (RotaTeq): 2 mL (6.7 to 12.4 x 10^7 PFU); 3 doses given 4 weeks apart; 1018 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 1018 participants (randomized) **Schedule:** 3 doses given at 4-week intervals
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms

TEQ Zaman 2010-AS *(Continued)*

	4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea – severe 7. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose (review included data from for the end of follow-up) Data on fever and vomiting were provided only on figure 2 and data could not be extracted reliably. **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4-fold) (review included data from after dose 2)
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) High-mortality countries
Notes	This trial was conducted in Bangladesh and Vietnam; data reported separately by country can be found under TEQ Zaman 2010-BGD and TEQ Zaman 2010-VNM. **Date:** March 29, 2007 to March 31, 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six".
Allocation concealment (selection bias)	Low risk	Quote: "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) All outcomes	Low risk	Participants and staff: Quote: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial". Researchers: Quote: "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) All outcomes	Low risk	Missing data balanced across groups

TEQ Zaman 2010-AS *(Continued)*

Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	No apparent other bias

TEQ Zaman 2010-BGD

Study characteristics	
Methods	RCT **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:** 1136 randomized **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 were no enrolment restrictions based on HIV status, although HIV testing was not done. **Exclusion criteria**: see above
Interventions	1. WC3 (RotaTeq): 2 mL (6.7 to 12.4 x 10^7 PFU); 3 doses given 4 weeks apart; 568 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 568 participants (randomized) **Schedule:** 3 doses given at a 4-week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea – severe

TEQ Zaman 2010-BGD *(Continued)*

	7. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose (review included data from for the end of follow-up) Data on fever and vomiting were provided only on figure 2 and data could not be extracted reliably. **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4 fold) (review included data from after dose 2)
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 High-mortality country
Notes	This trial was conducted in Bangladesh and Vietnam; this part presented data for the Bangladesh cohort; data reported separately for Vietnam can be found under TEQ Zaman 2010-VNM and data for both countries under TEQ Zaman 2010-AS. **Date:** March 29, 2007 to March 31, 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six".
Allocation concealment (selection bias)	Low risk	Quote: "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) All outcomes	Low risk	Participants and staff: Quote: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial". Researchers: Quote: "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) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	No apparent other bias

TEQ Zaman 2010-VNM

Study characteristics	
Methods	RCT **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:** 900 randomized **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 were no enrolment restrictions based on HIV status, although HIV testing was not done. **Exclusion criteria**: see above
Interventions	1. WC3 (RotaTeq): 2 mL (6.7 to 12.4 x 10^7 PFU); 3 doses given 4 weeks apart; 450 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 450 participants (randomized) **Schedule:** 3 doses given at 4-week intervals
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-hour period or forceful vomiting, or both, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea – severe 7. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose (review included data from for the end of follow-up) Data on fever and vomiting were provided only on figure 2 and data could not be extracted reliably. **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4-fold) (review included data from after dose 2)

TEQ Zaman 2010-VNM *(Continued)*

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 urban and peri-urban Nha Trang, Vietnam High-mortality country
Notes	This trial was conducted in Bangladesh and Vietnam; this part presented data for the Vietnam cohort. Data reported separately for Bangladesh can be found under TEQ Zaman 2010-BGD and data for both countries under TEQ Zaman 2010-AS. **Date:** March 29, 2007 to March 31, 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six".
Allocation concealment (selection bias)	Low risk	Quote: "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) All outcomes	Low risk	Participants and staff: Quote: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial". Researchers: Quote: "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) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	No apparent other bias

VAC Bhandari 2006-IND

Study characteristics

Methods	Phase I RCT **Length of follow-up:** 28 days

VAC Bhandari 2006-IND *(Continued)*

	Adverse event data collection methods: Caregivers reported any symptoms or illnesses on diary cards or to physician on-call 24 hours; physicians and field investigators visited participants twice daily the first 14 days.
Participants	**Number:** 90 enrolled, 90 randomized, 83 evaluable **Age range:** 8 weeks at enrolment and first dose **Inclusion criteria:** healthy, non-malnourished infants **Exclusion criteria:** Evidence of renal, cardiovascular, liver or other reticuloendothelial, neurological, gastrointestinal, haematologic, rheumatologic or immunologic disease
Interventions	Rotavac 1. Rotavac vaccine (116E) (10^5 FFU), n = 30 2. Rotavirus vaccine candidate I321, n = 30 3. Placebo, n = 30 **Schedule:** 1 dose given at 8 weeks of age
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause death 2. Intussusception 3. Serious adverse events 4. Reactogenicity (up to 14 days) **Outcomes to measure immunogenicity** 5. Immunogrnicity: seroconversion (4-fold rise in titre of IgA) 6. Immunogenicity: shedding
Immunization status	Infants were vaccinated with DPT, HepB and OPV separately from rotavirus vaccine.
Location	1 site (Delhi) in India High-mortality country
Notes	**Date:** January to May 2005 **Registration number:** NCT00280111; ISRCTN57452882 **Source of funding:** Bharat Biotech International Ltd. **Notes:** study arm administered vaccine candidate I321 was excluded from data analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "For randomisation, a sequence of codes was generated using Stata, version 8 (Statacorp, College Station, TX, USA) by a statistician not otherwise involved with the trial."
Allocation concealment (selection bias)	Low risk	Quote: "Two copies of the randomisation code were prepared; one was sent to the Division of Microbiology and Infectious Diseases (DMID) at the NIH under

VAC Bhandari 2006-IND *(Continued)*

		sealed cover, and the second was given to a physician, not otherwise involved in the study, for reconstituting the vaccine/placebo at the time of enrolment."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double-blind" Quote: "The placebo was constituted by adding a crystal of potassium permanganate to sodium bicarbonate buffer and appeared identical to the vaccines but did not contain the virus."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition; reasons for loss to follow-up were reported and evenly spread across groups.
Selective reporting (reporting bias)	Low risk	No indication of selective reporting; all outcomes in the trial register reported.
Other bias	Low risk	No apparent other bias

VAC Bhandari 2009-IND

Study characteristics	
Methods	RCT **Length of follow-up:** 12 weeks **Adverse event data collection methods:** Caregivers reported any symptoms or illnesses to physician on-call 24 hours; infants were visited at home daily the first 14 days after each administration.
Participants	**Number:** 369 enrolled and randomized; 367 received at least one dose **Age range:** 8 to 9 weeks **Inclusion criteria:** healthy infants **Exclusion criteria:** family without access to a telephone, unavailable for follow-up, weight-for-height z score of < 3 standard deviations, resided with an immunocompromised individual, born at a gestational age of < 37 weeks, major congenital abnormality, history of hospitalization for sepsis, pneumonia, or meningitis, diarrhoea in the previous 7 days, blood in stools any time after birth, need for daily medication, cardiovascular or neurological disease
Interventions	Rotavac 1. Rotavac vaccine (116E) (1 x 10^4 (low dose) or 1 x 10^5 FFU (high dose)), n = 185 2. Placebo, n = 184 **Schedule:** 3 doses given at 4-week intervals at 8, 12, and 16 weeks of age
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause death 2. Intussusception (level 1, Brighton definition) 3. Serious adverse events 4. Reactogenicity (up to 14 days) **Outcomes to measure immunogenicity** 5. Immunogenicity: shedding

VAC Bhandari 2009-IND *(Continued)*

	6. Immunogenicity: seroconversion (4-fold increase in IgA antibody titer to rotavirus)
Immunization status	Infants received 3 doses of DTP; OPV; and HepB at 6, 10, and 14 weeks of age.
Location	1 site (New Delhi) in India High-mortality country
Notes	**Date:** November 2006 to February 2008 **Registration number:** NCT00439660; ISRCTN57452882 **Source of funding:** Department of Biotechnology, Government of India and PATH

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Infants were assigned to either the vaccine or placebo groups in a 1:1 ratio with use of a randomization sequence generated by a statistician not otherwise involved with the study (Stata software, version 8.0) with a fixed block length of 4.
Allocation concealment (selection bias)	Low risk	Allocation concealment was achieved by using serially-numbered sealed opaque envelopes. One set of envelopes was available with the independent vaccine-dispensing team and another with the study data safety monitoring board.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study reported to be double-blind but no further details were reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intussusception data reported for all enrolled participants; immunogenicity and reactogenicity were not reported for all participants and the reason was not clear.
Selective reporting (reporting bias)	Low risk	No indication of selective outcome reporting
Other bias	Low risk	No apparent other bias

VAC Bhandari 2014-IND

Study characteristics

Methods	RCT **Length of follow-up:** up to 2 years of age **Adverse event data collection methods:** All participants were contacted weekly at home by trained field workers to identify gastroenteritis, signs and symptoms of suspected intussusception, hospitalizations, and other illnesses. In addition, families reported any adverse events.
Participants	**Number:** 6799 enrolled, randomized and received at least one dose **Age range:** 6 to 7 weeks at recruitment

VAC Bhandari 2014-IND *(Continued)*

	Inclusion criteria: parents consented to participation and had no plans to move out of the study area during the next 24 months. **Exclusion criteria:** infants were excluded if they had received a rotavirus vaccine, had documented immunodeficiency or chronic gastroenteritis or any other condition judged by the investigator as an exclusion criterion. Presence of any illness requiring hospital referral and diarrhoea on the day of enrolment was a temporary exclusion.
Interventions	Rotavac 1. Rotavac (ORV 116E) vaccine (1 x 10^5 FFU), n = 4532 2. Placebo, n = 2267 **Schedule:** 3 doses given at 4-week intervals (6 to 7 weeks, ≥ 10 weeks, and ≥ 14 weeks of age)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Severe rotavirus gastroenteritis (≥ 11 on the 20-point Vesikari scoring scale) 2. All-cause death 3. Intussusception (Brighton criteria, level 1) 4. Serious adverse events 5. Severe all-cause diarrhoea 6. Rotavirus diarrhoea: any severity **Outcomes to measure immunogenicity** 7. Seroconversion (4-fold rise in titre from paired serum samples)
Immunization status	Other childhood vaccines (DTPw, Hib, HepB, and OPV) given concurrently
Location	3 sites: Delhi, Pune, and Vellore in India High-mortality country
Notes	**Date:** March 2011 to November 2012 **Registration number:** NCT01305109; CTRI/2010/091/000102 **Source of funding:** The Department of Biotechnology, and Biotechnology Industry Research Assistance Council, Government of India; the Bill & Melinda Gates Foundation to PATH; Research Council of Norway; Department for International Development, UK; National Institutes of Health, USA; Bharat Biotech International Ltd. Moved from ongoing other NCT01305109 and other CTRI-091-000102

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed by Cenduit, LLC, Germany, with stratification by site, and a block size of 12.
Allocation concealment (selection bias)	Low risk	The letter code on the vaccine/placebo vial was masked with the participant identification number before sending the vial to the clinical co-ordinator administering the test article to the enrolled infant.

VAC Bhandari 2014-IND *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	The placebo was identical in content, packaging, and appearance to the vaccine but did not contain the virus.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 1% loss to follow-up
Selective reporting (reporting bias)	Low risk	No indication of selective reporting; all outcomes in the trial register reported
Other bias	Low risk	No apparent other bias

VAC Chandola 2017-IND

Study characteristics	
Methods	RCT **Length of follow-up:** 1 year **Adverse event data collection methods:** Daily contacts through telephone calls or home visit for 14 days after each dose. Thereafter, weekly contacts were made until infants were 1 year of age.
Participants	**Number:** 1356 enrolled and randomized; 1327 completed 1 year follow-up. **Age range:** 6 to 8 weeks **Inclusion criteria:** healthy infants whose parents were willing to participate and had no plans for moving away were eligible for enrolment. **Exclusion criteria:** had already received the first dose of the childhood vaccines or any other rotavirus vaccine, had immunodeficiency disease or chronic gastroenteritis disease, and/or any condition warranting exclusion by the investigator
Interventions	Rotavac 1. Rotavac vaccine, 1 x 10^4 FFU, in 3 production lots, n = 1017 2. Placebo, n= 339 **Schedule:** 3 doses given at a 4- to 8-week intervals (6–7 weeks, 10-< 14, and 14-< 18 weeks of age)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause death 2. Serious adverse events 3. Intussusception (level 1, Brighton criteria) 4. Reactogenicity **Outcomes to measure immunogenicity** 5. Immunogenicity: seroconversion (≥ 4 fold rise in IgA antibody titer to rotavirus)
Immunization status	Co-administered with EPI vaccines: OPV and combined DPT, HepB and Hib
Location	1 site in Delhi, India

VAC Chandola 2017-IND *(Continued)*

	High-mortality country
Notes	**Date:** May 2014 to August 2015 **Registration number:** CTRI/2014/05/004592 **Source of funding:** PATH, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done by Diagnosearch Life Sciences Pvt. Ltd. and the randomization list was available with an independent biostatistician".
Allocation concealment (selection bias)	Low risk	Central allocation Quote: "Randomization was done by Diagnosearch Life Sciences Pvt. Ltd. and the randomization list was available with an independent biostatistician".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The placebo was identical in content, packaging, and appearance to the vaccine. The study team received ROTAVAC® or placebo vials labeled with the subject Identification (ID) number to maintain blinding. The study team, vaccine administrators and laboratory personnel were not aware of the treatment status."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population was analysed for safety outcomes. Less than 5% loss to follow-up
Selective reporting (reporting bias)	Low risk	No indication of selective reporting; all outcomes in the trial register reported
Other bias	Low risk	No apparent other bias

AGE: acute gastroenteritis
ATP: according to protocol
BCG: bacillus Calmette-Guerin
BRV-PV: bovine rotavirus pentavalent vaccine
BRV-TV: bovine rotavirus tetravalent vaccine
$CCID_{50}$: cell culture infectious dose 50%
CD4: cluster differentiation 4 glycoprotein co-receptor
CDC: Centres for Disease Control and Prevention
CSL: Commonwealth Serum Laboratory
DNA: deoxyribonucleic acid
DTP(a/w/wcsl): diphtheria, tetanus, pertussis vaccine (acellular/whole-cell/whole cell Commonwealth Serum Laboratory)
eCRF: electronic case report form
EIA: enzyme-linked immunosorbent assay
ELISA: Enzyme Linked Immunosorbent Assay
EPI: Expanded Program on Immunization
FFU: focus-forming unit
GE: gastroenteritis
GI: gastrointestinal
GSK: GlaxoSmithKline
HBV: Hepatitis B vaccine
HepB: Hepatitis B
Hib: *Haemophilus* influenzae type B
HIV: human immunodeficiency virus
HRV: human rotavirus vaccine (Rotarix)

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID: identification
IgA: immunoglobulin A
IgG: immunoglobulin G
IMPAACT: International Maternal, Pediatric, and Adolescent AIDS Clinical Trial Network
IPV: inactivated polio vaccine
ITT: intention-to-treat
IU: infectious units
Kft: Korlatolt Felelossegu Tarsasag (Hungarian: limited company)
LAR: legally acceptable representative
MedDRA: Medical Dictionary for Regulatory Activities
n: number
N: number
OPV: oral poliovirus
P: p-value
PATH: Program for Appropriate Technology in Health
PFU: plaque-forming unit
PL-V-V: placebo-vaccine-vaccine
RAPID: Rotavirus Action Partnership for Immunization and Development programme
RCT: randomized controlled trial
RIX4414: Rotarix vaccine
RNA: ribonucleic acid
RT-PCR: reverse transcriptase-polymerase chain reaction
RV1: monovalent rotavirus vaccine (Rotarix)
RV5: pentavalent rotavirus vaccine (RotaTeq)
(S)AE: (serious) adverse event
SAS: Statistical Analysis system
SBIR: Small Business Innovation Research
SD: standard deviation
SE: standard error
tOPV: trivalent oral polio vaccine
V-PL-V: vaccine-placebo-vaccine
VRC: vaccine report card
WC3: WC3 rotavirus strain (RotaTeq)
WHO: World Health Organization

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

Study	Reason for exclusion
OTHER Abu-Elyazeed 2020	Not a relevant intervention/comparison: comparing different formulations (no placebo/control group)
OTHER Armah 2013	RCT of withdrawn RV vaccine RRV-TV
OTHER Bines 2015	Neonatal RV vaccine RV3-BB in development
OTHER Bines 2018	RCT of unlicensed neonatal RV3-BB rotavirus vaccine (ACTRN12612001282875)
OTHER Bucher 2012	Diagnostic test accuracy study
OTHER Cowley 2017	RCT of unlicensed neonatal RV3-BB rotavirus vaccine
OTHER Cowley 2019	Not relevant intervention: RV3-BB neonatal rotavirus vaccine
OTHER Dang 2012	RCT evaluating safety and immunogenicity of vaccine licensed in Vietnam (NCT01377571); vaccine not prequalified by the WHO

Study	Reason for exclusion
OTHER Ella 2018	All infants received rotavirus vaccine, and were randomized to Rotavac (116E) with or without buffering agent. (CTRI/2014/04/004548)
OTHER Groome 2017	RCT in infants of RV vaccine in development: parenteral P2-VP8-P[8] subunit RV vaccine (NCT02109484)
OTHER Groome 2020	Not relevant intervention: parenteral trivalent P2-VP8 subunit rotavirus vaccine
OTHER Kanchan 2020	No non-RV vaccine control/placebo in infant cohort (placebo group only for adults): RotaTeq vs. heat stable rotavirus vaccine (Hilleman Labs)
OTHER Rivera 2011	RCT; no placebo comparison
OTHER Salamanca de la Cueva 2020	Not relevant intervention/comparison: no placebo/control: PCV-free HRV or HRV
OTHER Xia 2020	Not relevant intervention: Lanzhou Lamb Rotavirus vaccine
OTHER Yin 2017	Oral RV vaccine (not specified, could be both Rotarix and RotaTeq) was administered before versus after other injected vaccines to compare injection site pain of the other vaccines.
RIX/TEQ Libster 2016	RCT of Rotarix and RotaTeq combined in different sequences
RIX Ali 2014	Comparing different age schedules of Rotarix
RIX Armah 2016	Comparing alternative dosing schedules
RIX Aziz 2020	No relevant outcomes: association of socioeconomic factors with diarrhoea in follow-up of included cluster-trial (RIX Zaman 2017-BGD)
RIX Dennehy 2008	RCT of Rotarix vaccine, but no placebo group reported
RIX Emperador 2016	No placebo group: Rotarix on a staggered versus concomitant schedule with other vaccines
RIX Gillard 2019	Not relevant intervention/comparison: DTP-IPV vaccine administered concomitantly or staggered with the liquid HRV (Rotarix) vaccine
RIX Kazi 2017	1 arm of an RCT (RIX Ali 2014) was included in this sub-study analysing histo-blood group antigens.
RIX Kompithra 2014	No placebo group: immunogenicity for 3 versus 5 doses Rotarix
RIX Lazarus 2017	All received RV vaccine with or without zinc and/or probiotic supplements
RIX Lee 2018	No relevant outcomes: immunogenicity for included RIX Colgate 2016-BGD rotavirus diarrhoea was also reported, but for smaller population than what we extracted in the review.
RIX Ramani 2016	No placebo group: Rotarix co-administered with IPV or with OPV was compared.
RIX Rojas 2007	Viral conversion on the same population of RIX Ruiz-Palac 06-LA/EU (included trial)
RIX Rongsen-Chandola 2014	Infants were breastfed versus not breastfed 30 mins prior and post-Rotarix administration. No placebo group
RIX Taddio 2015	To assess pain at injection site of other vaccines, participants were randomized to: 1. oral Rotarix then other injected vaccines then oral sucrose, or to

Study	Reason for exclusion
	2. oral sucrose then other injected vaccines then oral Rotarix.
RIX Williams 2021	No relevant outcomes: only immunogenicity outcomes for already included RIX Colgate 2016-BGD
RIX Zaman 2016	Study investigated co-administration of measles-rubella vaccines with RV vaccine.
SIIL Desai 2018	Not relevant intervention/comparison: no placebo/control group (non-inferiority study)
SIIL Hitchings 2020	No relevant outcomes: only immunogenicity outcomes for already included SIIL Isanaka 2017-NER
SIIL Kawade 2019	Not relevant intervention/comparison: no placebo/control arm
SIIL Rathi 2018	Not relevant intervention/comparison: no placebo/control group; non-inferiority trial
TEQ Ciarlet 2008	RCT of RotaTeq vaccine, but no placebo group reported
TEQ Haidara 2018	Not relevant intervention/comparison: no placebo/non-RV vaccine group: 3 vs 4 doses
TEQ Hemming-Harlo 2019	No relevant outcomes: long-term follow-up on type 1 diabetes, celiac disease, other specific autoimmune diseases for already included TEQ Vesikari 2006b-INT
TEQ Martinon-Torres 2017	RCT comparing standard versus alternative formulation of RotaTeq
TEQ Mo 2019	No relevant outcomes: only immunogenicity outcomes for already included TEQ Mo 2017-CHN
TEQ Saleh 2018	Standard versus alternative schedule RotaTeq (NCT01960725)
TEQ Saluja 2017	RCT of BRV-TV versus RotaTeq
TEQ Tugcu 2009	RCT of RotaTeq vaccine; no placebo group reported
TEQ Uprety 2017	Sub-study of TEQ Levin 2017-AF; this sub-study only included participants in the vaccine arm and compared HIV-positive to HIV-exposed but uninfected infants.
TEQ Vesikari 2011	RCT of RotaTeq and MenCC vaccines - concomitant or sequential administration; no placebo group reported
TEQ Weinberg 2017	Sub-study of selected participants from TEQ Levin 2017-AF, reporting only irrelevant outcomes for this review
VAC Ella 2019	Not relevant intervention/comparison: no placebo/non-RV vaccine group; non-inferiority trial

BRV-TV: bovine rotavirus tetravalent vaccine
DTP: diphtheria, tetanus, pertussis
HIV: human immunodeficiency virus
HRV: human rotavirus vaccine (Rotarix)
IPV: inactivated polio vaccine
MenCC: meningococcal conjugate C vaccine
OPV: oral polio vaccine
P2-VP8: P2-VP8 rotavirus subunits
PCV: porcine circovirus
RCT: randomized controlled trial
RRV-TV: rhesus rotavirus tetravalent vaccine
RV3-BB: virus developed from the human neonatal rotavirus strain RV3 (G3P[6])
WHO: World Health Organization

DATA AND ANALYSES

Comparison 1. Rotarix versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Rotavirus diarrhoea: severe (up to 1 year follow-up)	13	56598	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.16, 0.36]
1.1.1 Low-mortality countries	4	14976	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.03, 0.18]
1.1.2 Medium-mortality countries	4	31671	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.16, 0.29]
1.1.3 High-mortality countries	5	9951	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.28, 0.61]
1.2 Rotavirus diarrhoea: severe (2nd year of life)	10	38590	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.16, 0.49]
1.2.1 Low-mortality countries	4	14808	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.08, 0.20]
1.2.2 Medium-mortality countries	3	17733	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.17, 0.35]
1.2.3 High-mortality countries	3	6049	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.52, 1.29]
1.3 Rotavirus diarrhoea: severe (up to 2 years follow-up)	12	49092	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.13, 0.38]
1.3.1 Low-mortality countries	6	18145	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.07, 0.14]
1.3.2 Medium-mortality countries	3	23834	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.17, 0.29]
1.3.3 High-mortality countries	3	7113	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.51, 0.83]
1.4 All-cause diarrhoea: severe cases (up to 1 year follow-up)	6	35992	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.54, 0.79]
1.4.1 Low-mortality countries	1	3874	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.37, 0.61]
1.4.2 Medium-mortality countries	2	26479	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.52, 0.79]
1.4.3 High-mortality countries	3	5639	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.56, 0.95]
1.5 All-cause diarrhoea: severe cases (up to 2 years follow-up)	6	32350	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.55, 0.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.1 Low-mortality countries	2	6269	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.40, 0.60]
1.5.2 Medium-mortality countries	2	23317	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.50, 1.09]
1.5.3 High-mortality countries	2	2764	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.72, 0.96]
1.6 All-cause diarrhoea: severe episodes (up to 1 year follow-up)	1		Rate Ratio (IV, Random, 95% CI)	Totals not selected
1.6.1 Medium-mortality countries	1		Rate Ratio (IV, Random, 95% CI)	Totals not selected
1.7 All-cause diarrhoea: severe episodes (up to 2 years follow-up)	2		Rate Ratio (IV, Random, 95% CI)	Subtotals only
1.7.1 Low-mortality countries	1	10519	Rate Ratio (IV, Random, 95% CI)	0.70 [0.56, 0.86]
1.7.2 Medium-mortality countries	1	28572	Rate Ratio (IV, Random, 95% CI)	0.61 [0.53, 0.70]
1.8 All-cause death	30	105778	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.81, 1.30]
1.8.1 Low-mortality countries	10	20361	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.17, 2.88]
1.8.2 Medium-mortality countries	9	77043	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.89, 1.81]
1.8.3 High-mortality countries	11	8374	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.21]
1.9 All serious adverse events	31	103714	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.81, 0.95]
1.9.1 Low-mortality countries	12	18971	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.72, 1.10]
1.9.2 Medium-mortality countries	9	77069	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.76, 0.95]
1.9.3 High-mortality countries	10	7674	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.05]
1.10 Serious adverse events: intussusception	21	106973	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.52, 1.46]
1.10.1 Low-mortality countries	10	20773	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.52, 3.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10.2 Medium-mortality countries	6	75540	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.39, 1.32]
1.10.3 High-mortality countries	5	10660	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.06, 36.63]
1.11 Serious adverse events: Kawasaki disease	3	13117	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.29, 10.73]
1.12 Serious adverse events requiring hospitalization	2	63675	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.81, 0.96]
1.13 Rotavirus diarrhoea: of any severity (up to 2 months follow-up)	12	4294	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.66, 1.97]
1.13.1 Low-mortality countries	4	2061	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.23, 3.32]
1.13.2 Medium-mortality countries	1	444	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.07, 22.23]
1.13.3 High-mortality countries	7	1789	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.65, 2.22]
1.14 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)	10	19600	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.26, 0.50]
1.14.1 Low-mortality countries	3	4457	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.10, 0.24]
1.14.2 Medium-mortality countries	2	5192	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.26, 0.44]
1.14.3 High-mortality countries	5	9951	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.39, 0.68]
1.15 Rotavirus diarrhoea: of any severity (2nd year of life)	7	12744	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.32, 0.72]
1.15.1 Low-mortality countries	3	4393	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.22, 0.38]
1.15.2 Medium-mortality countries	2	3496	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.38, 1.24]
1.15.3 High-mortality countries	2	4855	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.36, 1.18]
1.16 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)	8	16143	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.25, 0.54]
1.16.1 Low-mortality countries	4	6878	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.18, 0.27]

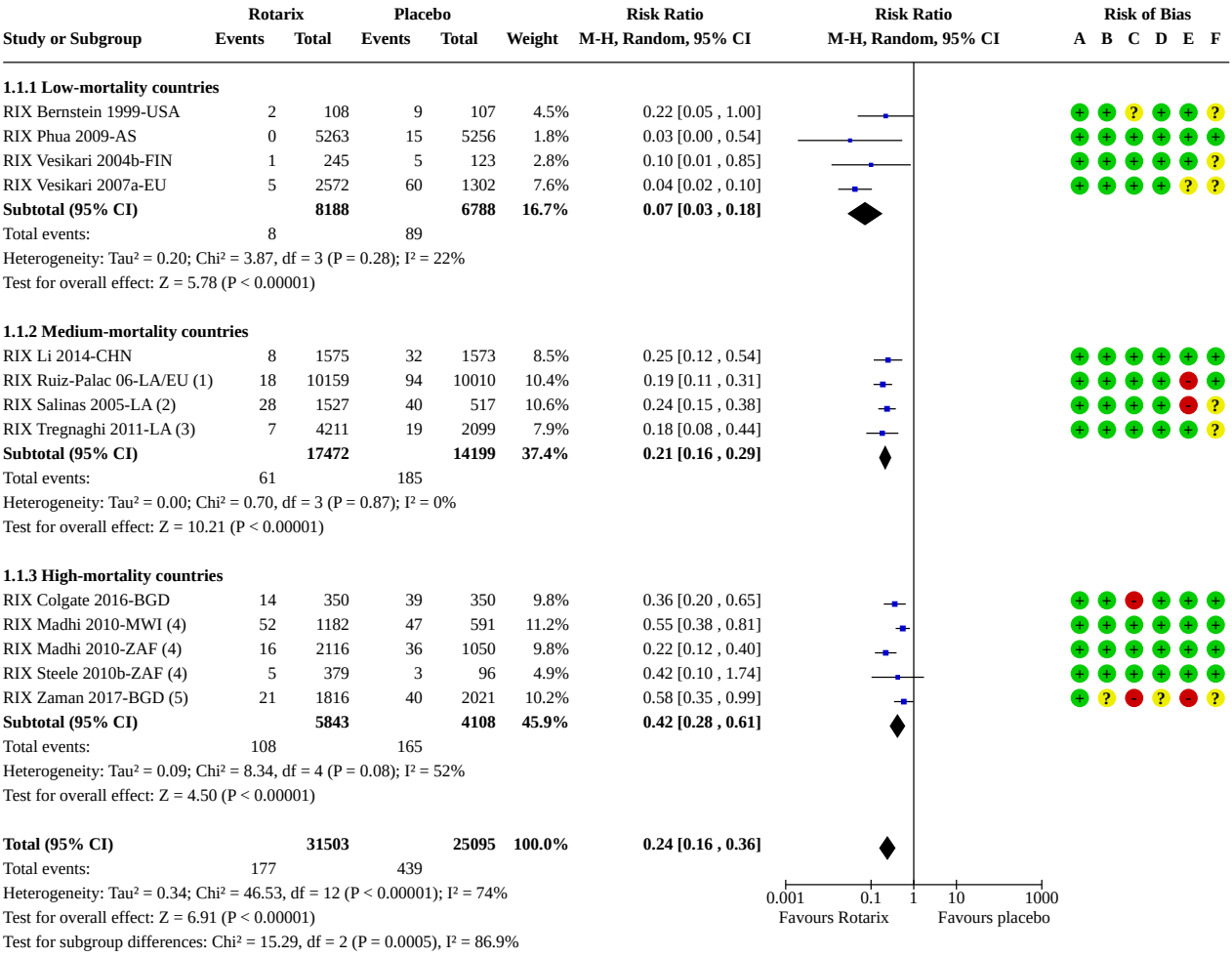
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16.2 Medium-mortality countries	2	3665	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.35, 0.59]
1.16.3 High-mortality countries	2	5600	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.32, 0.93]
1.17 All-cause diarrhoea: all cases (up to 2 months follow-up)	7	3132	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.73, 1.11]
1.17.1 Low-mortality countries	3	1906	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.59, 1.08]
1.17.2 Medium-mortality countries	1	444	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.46, 2.02]
1.17.3 High-mortality countries	3	782	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.74, 1.38]
1.18 All-cause diarrhoea: all cases (up to 1 year follow-up)	3	2944	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.84, 1.06]
1.18.1 Medium-mortality countries	2	2244	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 0.98]
1.18.2 High-mortality countries	1	700	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
1.19 All-cause diarrhoea: all cases (up to 2 years follow-up)	4	6454	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.88, 1.00]
1.19.1 Low-mortality countries	2	2789	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.65, 1.00]
1.19.2 Medium-mortality countries	2	3665	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.90, 1.01]
1.20 All-cause diarrhoea: all episodes (up to 1 year follow-up)	2		Rate Ratio (IV, Random, 95% CI)	0.98 [0.88, 1.10]
1.20.1 Medium-mortality countries	2		Rate Ratio (IV, Random, 95% CI)	0.98 [0.88, 1.10]
1.21 All-cause diarrhoea: all episodes (up to 2 years follow-up)	1		Rate Ratio (IV, Random, 95% CI)	1.02 [0.78, 1.33]
1.21.1 Low-mortality countries	1		Rate Ratio (IV, Random, 95% CI)	1.02 [0.78, 1.33]
1.22 All-cause hospitalizations (up to 2 years follow-up)	2	65646	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.27, 1.47]
1.22.1 Low-mortality countries	1	2421	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.15, 0.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.22.2 Medium-mortality countries	1	63225	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.81, 0.96]
1.23 Rotavirus diarrhoea: requiring hospitalization	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.23.1 Up to 1 year follow-up (at least 1 rotavirus season)	8	48718	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.09, 0.33]
1.23.2 Up to 2 years follow-up (at least 2 rotavirus seasons)	7	35331	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.11, 0.22]
1.24 Rotavirus diarrhoea: requiring medical attention	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.24.1 Up to 1 year follow-up (at least 1 rotavirus season)	1	3874	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.04, 0.16]
1.24.2 Up to 2 years follow-up (at least 2 rotavirus seasons)	3	7017	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.16, 0.31]
1.25 All-cause diarrhoea: cases requiring hospitalization	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.25.1 Up to one year of follow-up (at least 1 rotavirus season)	3	20703	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.35, 0.83]
1.25.2 Second year of follow-up (at least 2 rotavirus seasons)	2	14367	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.27, 0.99]
1.26 All-cause diarrhoea: episodes requiring hospitalization	1		Rate Ratio (IV, Random, 95% CI)	Subtotals only
1.26.1 Up to 1 year of follow-up (at least 1 rotavirus season)	1		Rate Ratio (IV, Random, 95% CI)	0.58 [0.47, 0.71]
1.26.2 Second year of follow-up (at least 2 rotavirus seasons)	1		Rate Ratio (IV, Random, 95% CI)	0.53 [0.46, 0.61]
1.27 Reactogenicity: fever	28		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.27.1 After dose 1	25	16192	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.97, 1.17]
1.27.2 After dose 2	24	15630	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
1.27.3 After dose 3	4	1390	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.13]
1.27.4 End of follow-up	18	11926	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.28 Reactogenicity: diarrhoea	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.28.1 After dose 1	25	18732	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.88, 1.17]
1.28.2 After dose 2	24	15630	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.86, 1.21]
1.28.3 After dose 3	4	1390	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.35, 1.36]
1.28.4 End of follow-up	17	14305	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.08]
1.29 Reactogenicity: vomiting	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.29.1 After dose 1	25	18732	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.12]
1.29.2 After dose 2	24	15630	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.81, 1.05]
1.29.3 After dose 3	4	1390	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.71, 2.50]
1.29.4 End of follow-up	17	14305	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.04]
1.30 Adverse events requiring discontinuation (end of follow-up)	26	94980	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.82, 1.25]
1.31 Dropouts before the end of the trial	28	93106	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.90, 0.99]
1.32 Subgroup analysis: rotavirus diarrhoea of any severity (by G- or P-type)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.32.1 G1	7	31618	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.13, 0.47]
1.32.2 G2	7	31618	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.32, 0.56]
1.32.3 G3	5	9914	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.06, 0.29]
1.32.4 G4	3	6666	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.09, 0.49]
1.32.5 G9	5	13651	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.26, 0.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.32.6 G12	1	3837	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.28, 1.04]
1.32.7 P4	3	4685	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.17, 1.31]
1.32.8 P6	2	3937	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.28, 2.90]
1.32.9 P8	3	4685	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.16, 1.04]
1.33 Subgroup analysis: severe cases of rotavirus diarrhoea (by G- or P-type)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.33.1 G1	9	51229	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.10, 0.34]
1.33.2 G2	9	53013	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.18, 0.45]
1.33.3 G3	8	45296	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.09, 0.34]
1.33.4 G4	3	26464	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.04, 0.78]
1.33.5 G8	2	4417	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.02, 2.37]
1.33.6 G9	10	53740	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.13, 0.25]
1.33.7 G12	2	4417	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.23, 0.97]
1.33.8 P4	5	37206	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.20, 0.73]
1.33.9 P6	3	24586	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.20, 0.89]
1.33.10 P8	5	31644	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.14, 0.41]
1.34 Subgroup analysis: rotavirus diarrhoea in malnourished children	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.34.1 Up to 1 year of follow-up (at least 1 rotavirus season)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.35 Subgroup analysis: rotavirus diarrhoea in HIV-infected children	1	100	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.26, 3.78]

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



Footnotes

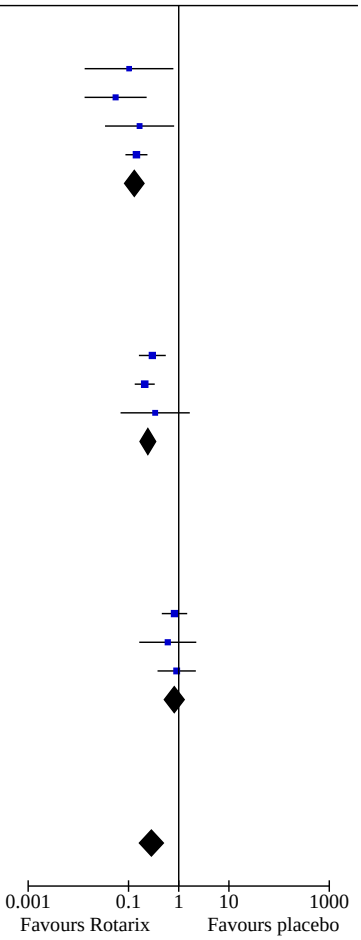
(1) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Honduras, Nicaragua, Venezuela.
(2) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela.
(3) Multinational study: mainly medium-mortality countries (n=4) but also two high-mortality countries: Dominican Republic and Honduras.
(4) 2 or 3 doses
(5) Adjusted for clustering: design effect of 2.53, villages randomised to Rotarix versus no intervention, true sample size: n=10,108

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.2. Comparison 1: Rotarix versus placebo, Outcome 2: Rotavirus diarrhoea: severe (2nd year of life)

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Low-mortality countries						
RIX Bernstein 1999-USA	1	91	10	93	5.0%	0.10 [0.01 , 0.78]
RIX Phua 2009-AS	2	5221	36	5194	7.6%	0.06 [0.01 , 0.23]
RIX Vesikari 2004b-FIN	2	241	6	120	6.8%	0.17 [0.03 , 0.81]
RIX Vesikari 2007a-EU	19	2554	67	1294	13.8%	0.14 [0.09 , 0.24]
Subtotal (95% CI)		**8107**		**6701**	**33.2%**	**0.13 [0.08 , 0.20]**
Total events:	24		119			
Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 3 (P = 0.61); I² = 0%						
Test for overall effect: Z = 8.98 (P < 0.00001)						
1.2.2 Medium-mortality countries						
RIX Li 2014-CHN	13	1500	43	1479	13.1%	0.30 [0.16 , 0.55]
RIX Ruiz-Palac 06-LA/EU (1)	22	7175	103	7062	14.1%	0.21 [0.13 , 0.33]
RIX Salinas 2005-LA (2)	3	386	3	131	6.8%	0.34 [0.07 , 1.66]
Subtotal (95% CI)		**9061**		**8672**	**34.0%**	**0.24 [0.17 , 0.35]**
Total events:	38		149			
Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 7.74 (P < 0.00001)						
1.2.3 High-mortality countries						
RIX Madhi 2010-MWI (3)	30	814	17	380	13.3%	0.82 [0.46 , 1.47]
RIX Madhi 2010-ZAF (3)	5	686	4	332	8.3%	0.60 [0.16 , 2.24]
RIX Zaman 2017-BGD (4)	9	1816	11	2021	11.2%	0.91 [0.38 , 2.19]
Subtotal (95% CI)		**3316**		**2733**	**32.8%**	**0.82 [0.52 , 1.29]**
Total events:	44		32			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**20484**		**18106**	**100.0%**	**0.29 [0.16 , 0.49]**
Total events:	106		300			
Heterogeneity: Tau² = 0.50; Chi² = 36.78, df = 9 (P < 0.0001); I² = 76%						
Test for overall effect: Z = 4.48 (P < 0.00001)						
Test for subgroup differences: Chi² = 33.17, df = 2 (P < 0.00001), I² = 94.0%						



Footnotes

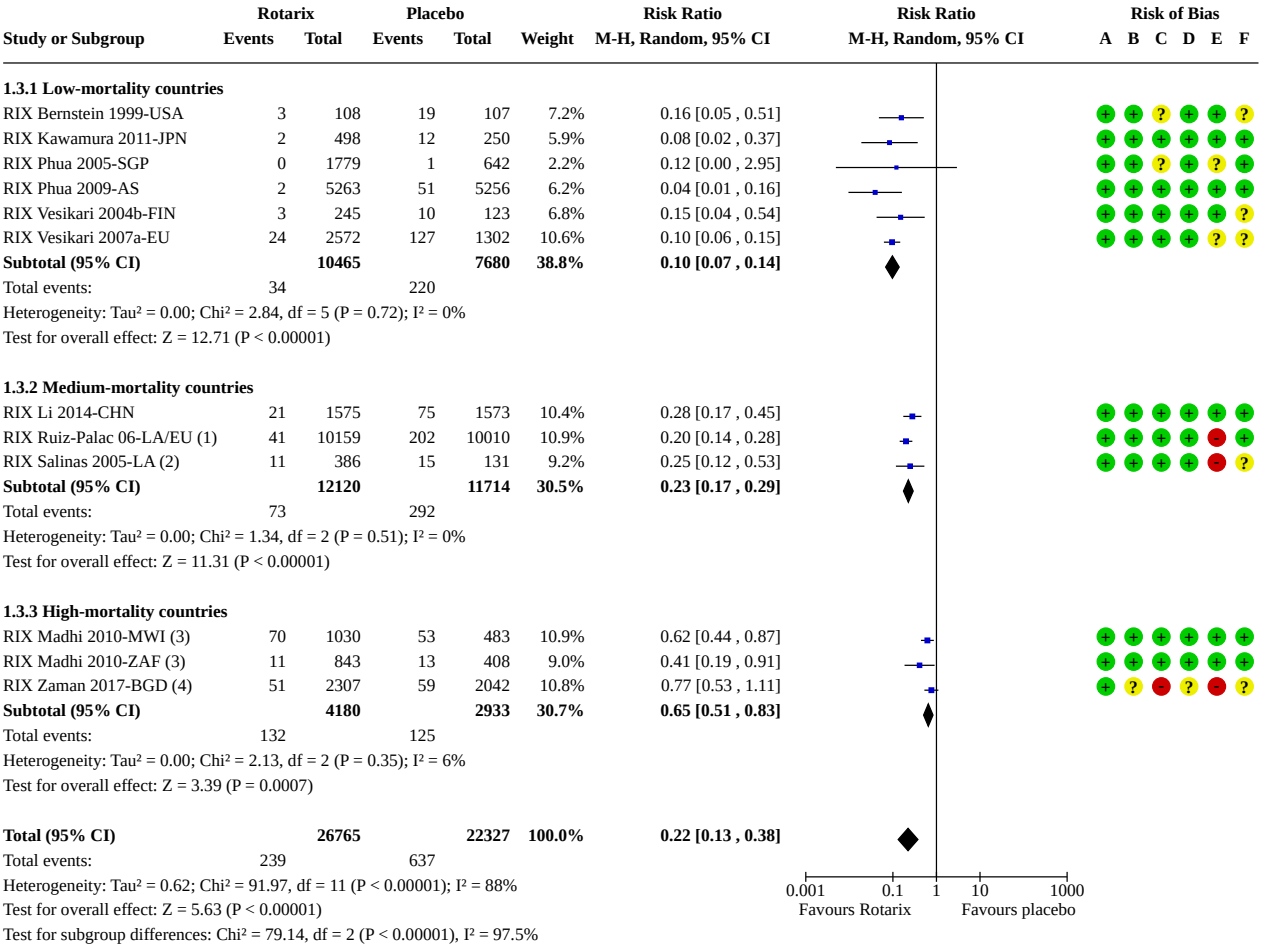
(1) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Honduras, Nicaragua, Venezuela.

(2) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela.

(3) 2 or 3 doses

(4) Adjusted for clustering: design effect of 2.53, villages randomised to Rotarix versus no intervention, true sample size: n=10,108.

Analysis 1.3. Comparison 1: Rotarix versus placebo, Outcome 3: Rotavirus diarrhoea: severe (up to 2 years follow-up)



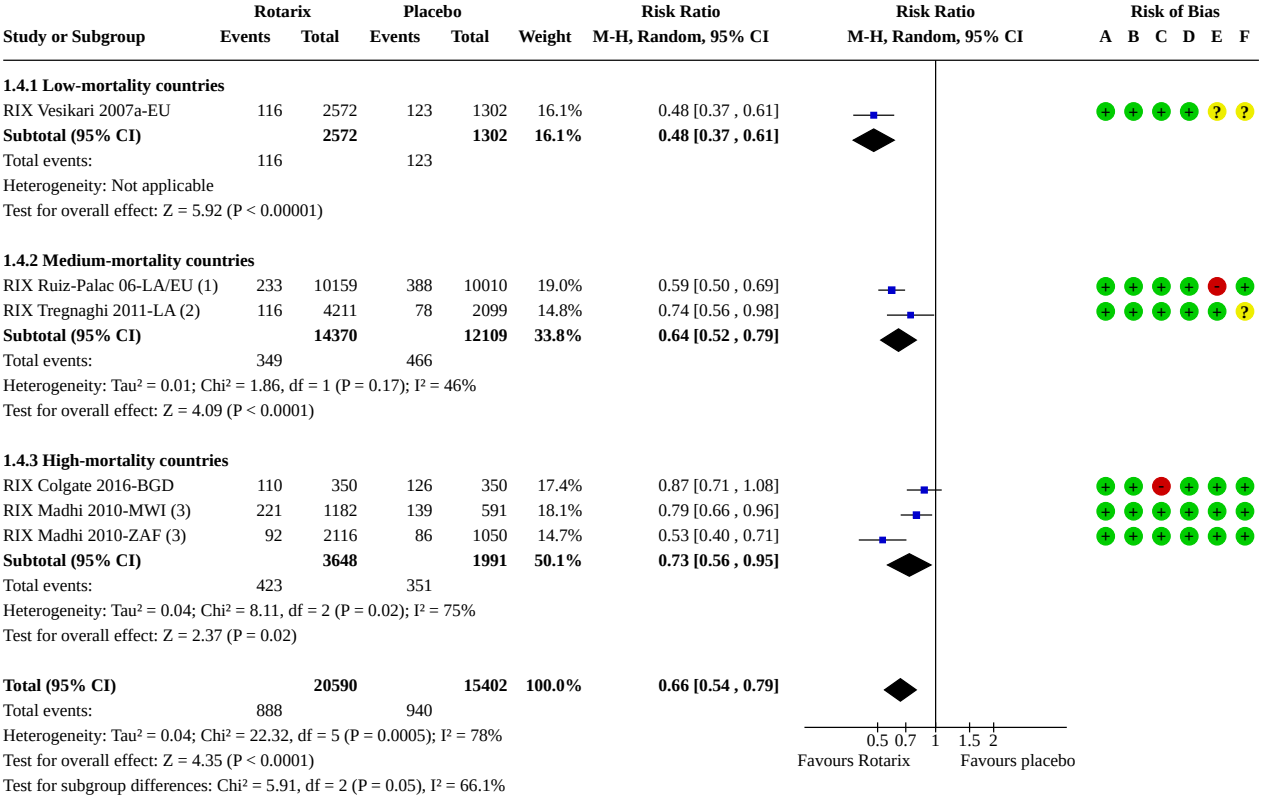
Footnotes

(1) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Honduras, Nicaragua, Venezuela.
(2) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela.
(3) 2 or 3 doses
(4) Adjusted for clustering: design effect of 2.53, villages randomised to Rotarix versus no intervention, true sample size: n=11,004

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

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



Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.4.1 Low-mortality countries												
RIX Vesikari 2007a-EU	116	2572	123	1302	16.1%	0.48 [0.37 , 0.61]	+	+	+	+	?	?
Subtotal (95% CI)		**2572**		**1302**	**16.1%**	**0.48 [0.37 , 0.61]**						
Total events:	116		123									
Heterogeneity: Not applicable												
Test for overall effect: Z = 5.92 (P < 0.00001)												
1.4.2 Medium-mortality countries												
RIX Ruiz-Palac 06-LA/EU (1)	233	10159	388	10010	19.0%	0.59 [0.50 , 0.69]	+	+	+	+	-	+
RIX Tregnaghi 2011-LA (2)	116	4211	78	2099	14.8%	0.74 [0.56 , 0.98]	+	+	+	+	+	?
Subtotal (95% CI)		**14370**		**12109**	**33.8%**	**0.64 [0.52 , 0.79]**						
Total events:	349		466									
Heterogeneity: Tau² = 0.01; Chi² = 1.86, df = 1 (P = 0.17); I² = 46%												
Test for overall effect: Z = 4.09 (P < 0.0001)												
1.4.3 High-mortality countries												
RIX Colgate 2016-BGD	110	350	126	350	17.4%	0.87 [0.71 , 1.08]	+	+	-	+	+	+
RIX Madhi 2010-MWI (3)	221	1182	139	591	18.1%	0.79 [0.66 , 0.96]	+	+	+	+	+	+
RIX Madhi 2010-ZAF (3)	92	2116	86	1050	14.7%	0.53 [0.40 , 0.71]	+	+	+	+	+	+
Subtotal (95% CI)		**3648**		**1991**	**50.1%**	**0.73 [0.56 , 0.95]**						
Total events:	423		351									
Heterogeneity: Tau² = 0.04; Chi² = 8.11, df = 2 (P = 0.02); I² = 75%												
Test for overall effect: Z = 2.37 (P = 0.02)												
Total (95% CI)		**20590**		**15402**	**100.0%**	**0.66 [0.54 , 0.79]**						
Total events:	888		940									
Heterogeneity: Tau² = 0.04; Chi² = 22.32, df = 5 (P = 0.0005); I² = 78%												
Test for overall effect: Z = 4.35 (P < 0.0001)												
Test for subgroup differences: Chi² = 5.91, df = 2 (P = 0.05), I² = 66.1%												

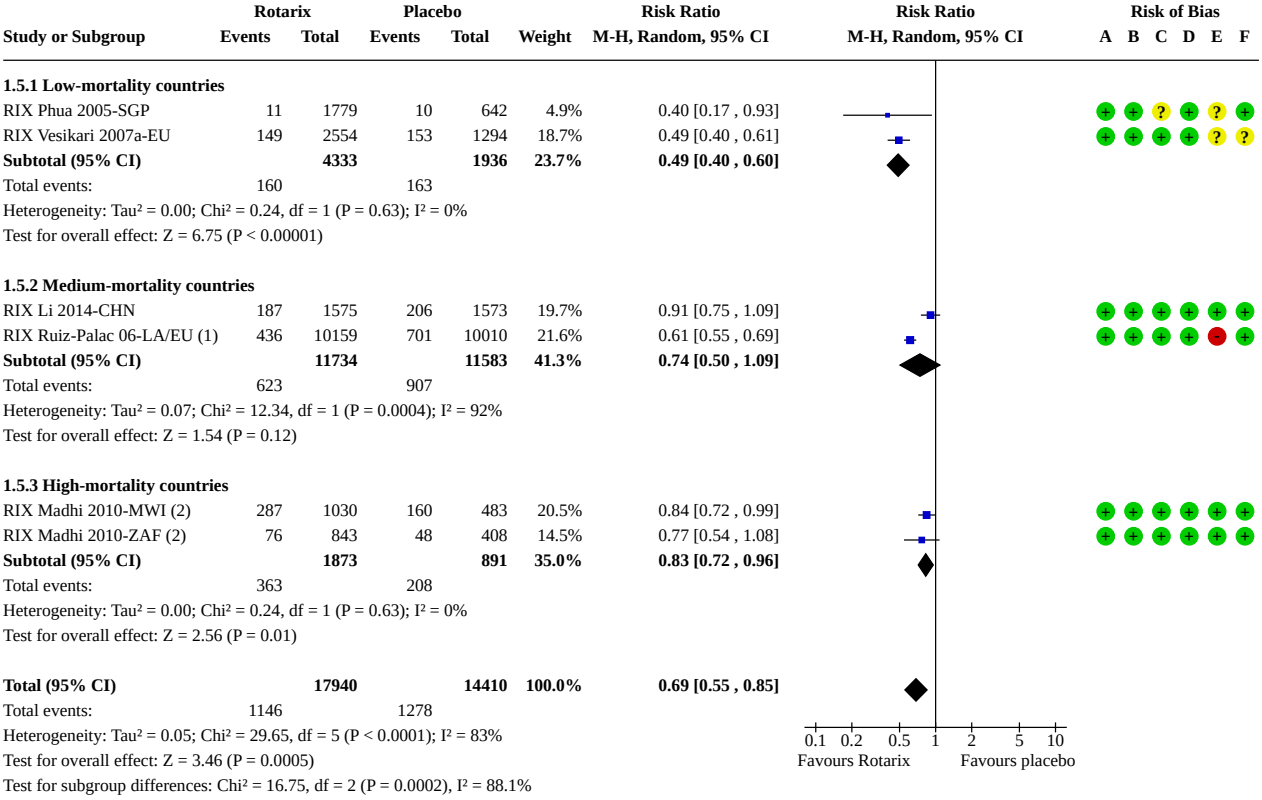
Footnotes

(1) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Honduras, Nicaragua, Venezuela
(2) Multinational study: mainly medium-mortality countries (n=4) but also two high-mortality countries: Dominican Republic and Honduras
(3) 2 or 3 doses

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.5. Comparison 1: Rotarix versus placebo, Outcome 5: All-cause diarrhoea: severe cases (up to 2 years follow-up)



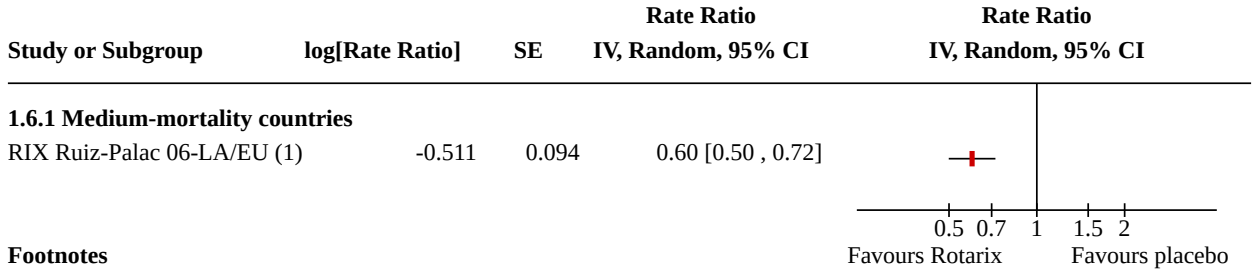
Footnotes

(1) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Honduras, Nicaragua, Venezuela
(2) 2 or 3 doses

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

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

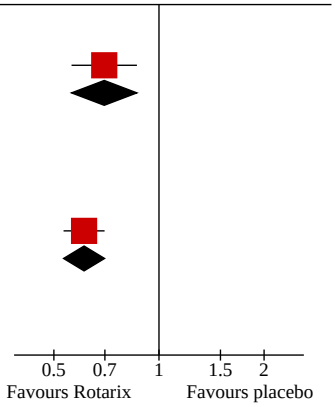


Footnotes

(1) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Hondu

Analysis 1.7. Comparison 1: Rotarix versus placebo, Outcome 7: All-cause diarrhoea: severe episodes (up to 2 years follow-up)

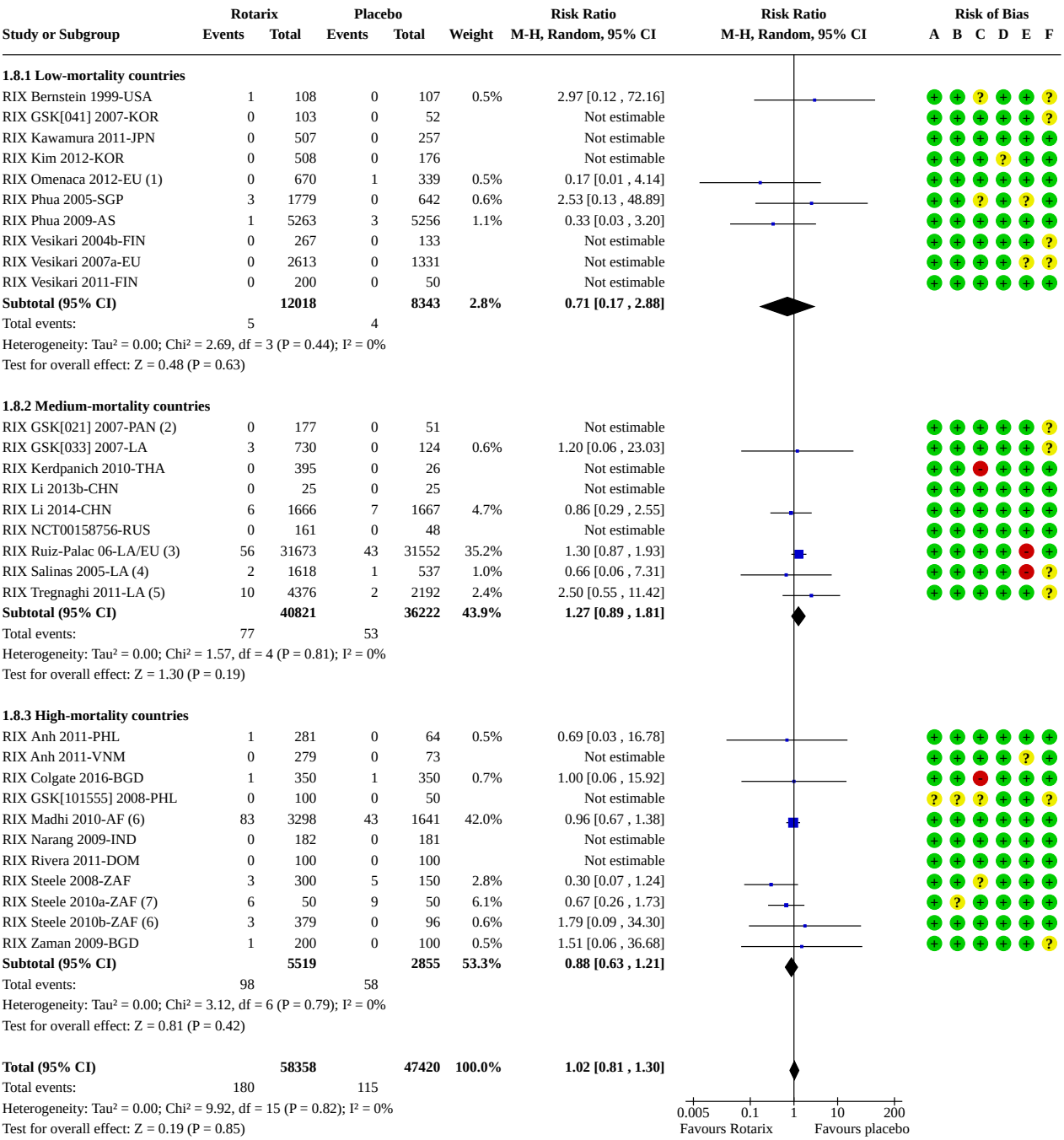
Study or Subgroup	log[Rate Ratio]	SE	Rotarix Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
1.7.1 Low-mortality countries						
RIX Phua 2009-AS	-0.361	0.11	5263	5256	100.0%	0.70 [0.56 , 0.86]
Subtotal (95% CI)			**5263**	**5256**	**100.0%**	**0.70 [0.56 , 0.86]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.28 (P = 0.001)						
1.7.2 Medium-mortality countries						
RIX Ruiz-Palac 06-LA/EU (1)	-0.494	0.069	14410	14162	100.0%	0.61 [0.53 , 0.70]
Subtotal (95% CI)			**14410**	**14162**	**100.0%**	**0.61 [0.53 , 0.70]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.16 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.05, df = 1 (P = 0.31), I² = 4.7%						



Footnotes

(1) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Honduras, Nicaragua, Venezuela

Analysis 1.8. Comparison 1: Rotarix versus placebo, Outcome 8: All-cause death



Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.8.1 Low-mortality countries							
RIX Bernstein 1999-USA	1	108	0	107	0.5%	2.97 [0.12 , 72.16]	+ + ? + + ?
RIX GSK[041] 2007-KOR	0	103	0	52		Not estimable	+ + + + + ?
RIX Kawamura 2011-JPN	0	507	0	257		Not estimable	+ + + + + +
RIX Kim 2012-KOR	0	508	0	176		Not estimable	+ + + ? + +
RIX Omenaca 2012-EU (1)	0	670	1	339	0.5%	0.17 [0.01 , 4.14]	+ + + + + +
RIX Phua 2005-SGP	3	1779	0	642	0.6%	2.53 [0.13 , 48.89]	+ + ? + ? +
RIX Phua 2009-AS	1	5263	3	5256	1.1%	0.33 [0.03 , 3.20]	+ + + + + +
RIX Vesikari 2004b-FIN	0	267	0	133		Not estimable	+ + + + + ?
RIX Vesikari 2007a-EU	0	2613	0	1331		Not estimable	+ + + + ? ?
RIX Vesikari 2011-FIN	0	200	0	50		Not estimable	+ + + + + +
Subtotal (95% CI)		**12018**		**8343**	**2.8%**	**0.71 [0.17 , 2.88]**	
Total events:	5		4				
Heterogeneity: Tau² = 0.00; Chi² = 2.69, df = 3 (P = 0.44); I² = 0%							
Test for overall effect: Z = 0.48 (P = 0.63)							
1.8.2 Medium-mortality countries							
RIX GSK[021] 2007-PAN (2)	0	177	0	51		Not estimable	+ + + + + ?
RIX GSK[033] 2007-LA	3	730	0	124	0.6%	1.20 [0.06 , 23.03]	+ + + + + ?
RIX Kerdpanich 2010-THA	0	395	0	26		Not estimable	+ + - + + +
RIX Li 2013b-CHN	0	25	0	25		Not estimable	+ + + + + +
RIX Li 2014-CHN	6	1666	7	1667	4.7%	0.86 [0.29 , 2.55]	+ + + + + +
RIX NCT00158756-RUS	0	161	0	48		Not estimable	+ + + + + +
RIX Ruiz-Palac 06-LA/EU (3)	56	31673	43	31552	35.2%	1.30 [0.87 , 1.93]	+ + + + - +
RIX Salinas 2005-LA (4)	2	1618	1	537	1.0%	0.66 [0.06 , 7.31]	+ + + + - ?
RIX Tregnaghi 2011-LA (5)	10	4376	2	2192	2.4%	2.50 [0.55 , 11.42]	+ + + + + ?
Subtotal (95% CI)		**40821**		**36222**	**43.9%**	**1.27 [0.89 , 1.81]**	
Total events:	77		53				
Heterogeneity: Tau² = 0.00; Chi² = 1.57, df = 4 (P = 0.81); I² = 0%							
Test for overall effect: Z = 1.30 (P = 0.19)							
1.8.3 High-mortality countries							
RIX Anh 2011-PHL	1	281	0	64	0.5%	0.69 [0.03 , 16.78]	+ + + + + +
RIX Anh 2011-VNM	0	279	0	73		Not estimable	+ + + + ? +
RIX Colgate 2016-BGD	1	350	1	350	0.7%	1.00 [0.06 , 15.92]	+ + - + + +
RIX GSK[101555] 2008-PHL	0	100	0	50		Not estimable	? ? ? + + ?
RIX Madhi 2010-AF (6)	83	3298	43	1641	42.0%	0.96 [0.67 , 1.38]	+ + + + + +
RIX Narang 2009-IND	0	182	0	181		Not estimable	+ + + + + +
RIX Rivera 2011-DOM	0	100	0	100		Not estimable	+ + + + + +
RIX Steele 2008-ZAF	3	300	5	150	2.8%	0.30 [0.07 , 1.24]	+ + ? + + +
RIX Steele 2010a-ZAF (7)	6	50	9	50	6.1%	0.67 [0.26 , 1.73]	+ ? + + + +
RIX Steele 2010b-ZAF (6)	3	379	0	96	0.6%	1.79 [0.09 , 34.30]	+ + + + + +
RIX Zaman 2009-BGD	1	200	0	100	0.5%	1.51 [0.06 , 36.68]	+ + + + + ?
Subtotal (95% CI)		**5519**		**2855**	**53.3%**	**0.88 [0.63 , 1.21]**	
Total events:	98		58				
Heterogeneity: Tau² = 0.00; Chi² = 3.12, df = 6 (P = 0.79); I² = 0%							
Test for overall effect: Z = 0.81 (P = 0.42)							
Total (95% CI)		**58358**		**47420**	**100.0%**	**1.02 [0.81 , 1.30]**	
Total events:	180		115				
Heterogeneity: Tau² = 0.00; Chi² = 9.92, df = 15 (P = 0.82); I² = 0%							
Test for overall effect: Z = 0.19 (P = 0.85)							
Test for subgroup differences: Chi² = 2.55, df = 2 (P = 0.28), I² = 21.5%							

Footnotes

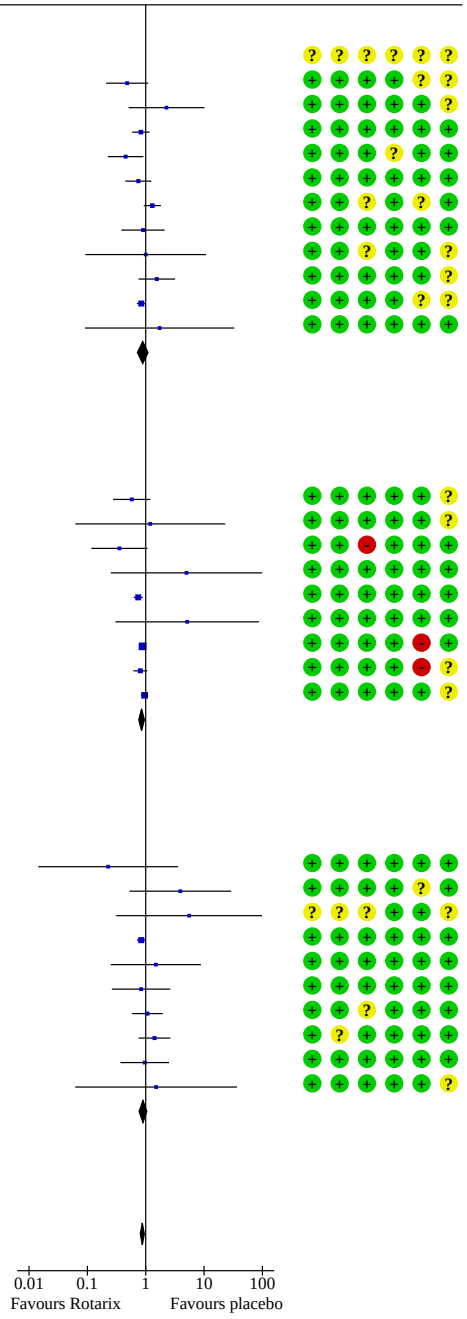
(1) pre-term infants
(2) 3 doses
(3) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Honduras, Nicaragua, Venezuela
(4) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela
(5) Multinational study: mainly medium-mortality countries (n=4) but also two high-mortality countries: Dominican Republic and Honduras
(6) 2 or 3 doses
(7) HIV-positive infants receiving 3 doses

Risk of bias legend

Analysis 1.8. (Continued)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.9. Comparison 1: Rotarix versus placebo, Outcome 9: All serious adverse events



Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Low-mortality countries						
RIX Bernstein 1998-USA	0	21	0	20		Not estimable
RIX Dennehy 2005-NA	15	421	8	108	0.9%	0.48 [0.21 , 1.10]
RIX GSK[041] 2007-KOR	9	103	2	52	0.3%	2.27 [0.51 , 10.14]
RIX Kawamura 2011-JPN	72	508	44	257	4.5%	0.83 [0.59 , 1.17]
RIX Kim 2012-KOR	17	508	13	176	1.2%	0.45 [0.22 , 0.91]
RIX Omenaca 2012-EU (1)	34	670	23	339	2.2%	0.75 [0.45 , 1.25]
RIX Phua 2005-SGP	144	1811	40	653	4.6%	1.30 [0.93 , 1.82]
RIX Phua 2009-AS	10	4272	11	4226	0.8%	0.90 [0.38 , 2.12]
RIX Vesikari 2004a-FIN	2	128	1	64	0.1%	1.00 [0.09 , 10.82]
RIX Vesikari 2004b-FIN	28	267	9	133	1.2%	1.55 [0.75 , 3.19]
RIX Vesikari 2007a-EU	290	2646	176	1348	11.8%	0.84 [0.70 , 1.00]
RIX Vesikari 2011-FIN	3	193	0	47	0.1%	1.73 [0.09 , 32.97]
Subtotal (95% CI)		**11548**		**7423**	**27.7%**	**0.89 [0.72 , 1.10]**
Total events:	624		327			
Heterogeneity: Tau² = 0.04; Chi² = 15.50, df = 10 (P = 0.11); I² = 35%						
Test for overall effect: Z = 1.10 (P = 0.27)						
1.9.2 Medium-mortality countries						
RIX GSK[021] 2007-PAN (2)	18	177	9	51	1.1%	0.58 [0.28 , 1.20]
RIX GSK[033] 2007-LA	3	730	0	124	0.1%	1.20 [0.06 , 23.03]
RIX Kerdpanich 2010-THA	11	396	4	51	0.5%	0.35 [0.12 , 1.07]
RIX Li 2013b-CHN	2	25	0	25	0.1%	5.00 [0.25 , 99.16]
RIX Li 2014-CHN	183	1666	246	1667	11.5%	0.74 [0.62 , 0.89]
RIX NCT00158756-RUS	8	161	0	48	0.1%	5.14 [0.30 , 87.50]
RIX Ruiz-Palac 06-LA/EU (3)	928	31673	1047	31552	20.5%	0.88 [0.81 , 0.96]
RIX Salinas 2005-LA (4)	156	1618	64	537	6.5%	0.81 [0.62 , 1.06]
RIX Tregnaghi 2011-LA (5)	505	4376	265	2192	14.8%	0.95 [0.83 , 1.10]
Subtotal (95% CI)		**40822**		**36247**	**55.2%**	**0.85 [0.76 , 0.95]**
Total events:	1814		1635			
Heterogeneity: Tau² = 0.01; Chi² = 11.62, df = 8 (P = 0.17); I² = 31%						
Test for overall effect: Z = 2.88 (P = 0.004)						
1.9.3 High-mortality countries						
RIX Anh 2011-PHL	1	281	1	64	0.1%	0.23 [0.01 , 3.59]
RIX Anh 2011-VNM	15	279	1	73	0.2%	3.92 [0.53 , 29.23]
RIX GSK[101555] 2008-PHL	5	100	0	50	0.1%	5.55 [0.31 , 98.50]
RIX Madhi 2010-AF (6)	319	3298	189	1641	12.2%	0.84 [0.71 , 1.00]
RIX Narang 2009-IND	3	182	2	181	0.2%	1.49 [0.25 , 8.82]
RIX Rivera 2011-DOM	5	100	6	100	0.5%	0.83 [0.26 , 2.64]
RIX Steele 2008-ZAF	30	300	14	150	1.6%	1.07 [0.59 , 1.96]
RIX Steele 2010a-ZAF (7)	17	50	12	50	1.5%	1.42 [0.76 , 2.65]
RIX Steele 2010b-ZAF (6)	19	379	5	96	0.7%	0.96 [0.37 , 2.51]
RIX Zaman 2009-BGD	1	200	0	100	0.1%	1.51 [0.06 , 36.68]
Subtotal (95% CI)		**5169**		**2505**	**17.1%**	**0.90 [0.77 , 1.05]**
Total events:	415		230			
Heterogeneity: Tau² = 0.00; Chi² = 8.00, df = 9 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.16)						
Total (95% CI)		**57539**		**46175**	**100.0%**	**0.87 [0.81 , 0.95]**
Total events:	2853		2192			
Heterogeneity: Tau² = 0.01; Chi² = 35.23, df = 29 (P = 0.20); I² = 18%						
Test for overall effect: Z = 3.30 (P = 0.0010)						
Test for subgroup differences: Chi² = 0.37, df = 2 (P = 0.83), I² = 0%						

Footnotes

(1) pre-term infants
(2) 3 doses
(3) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Honduras, Nicaragua, Venezuela
(4) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela
(5) Multinational study: mainly medium-mortality countries (n=4) but also two high-mortality countries: Dominican Republic and Honduras
(6) 2 or 3 doses
(7) HIV-positive infants receiving 3 doses

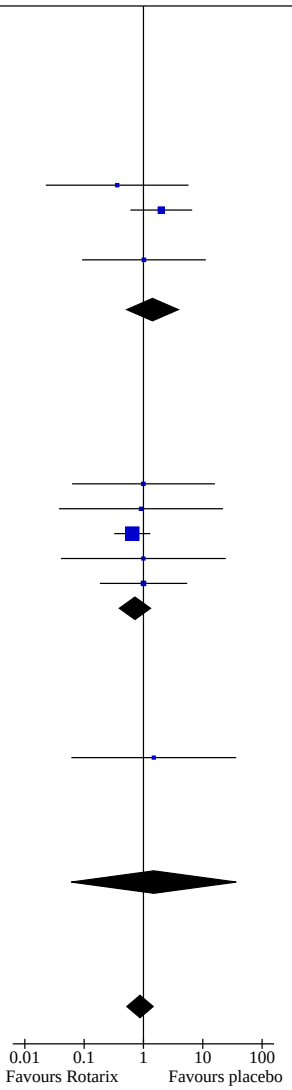
Analysis 1.9. (Continued)

(7) HIV-positive infants receiving 3 doses

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.10. Comparison 1: Rotarix versus placebo, Outcome 10: Serious adverse events: intussusception

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.10.1 Low-mortality countries							
RIX Dennehy 2005-NA	0	421	0	108		Not estimable	+ + + + ? ?
RIX GSK[041] 2007-KOR	0	103	0	52		Not estimable	+ + + + + ?
RIX Kawamura 2011-JPN	0	507	0	257		Not estimable	+ + + + + +
RIX Kim 2012-KOR	0	508	0	176		Not estimable	+ + + ? + +
RIX Omenaca 2012-EU (1)	0	670	0	339		Not estimable	+ + + + + +
RIX Phua 2005-SGP	1	1811	1	653	3.4%	0.36 [0.02 , 5.76]	+ + ? + ? +
RIX Phua 2009-AS	8	5263	4	5256	18.2%	2.00 [0.60 , 6.63]	+ + + + + +
RIX Vesikari 2004b-FIN	0	270	0	135		Not estimable	+ + + + + ?
RIX Vesikari 2007a-EU	2	2646	1	1348	4.5%	1.02 [0.09 , 11.23]	+ + + + ? ?
RIX Vesikari 2011-FIN	0	200	0	50		Not estimable	+ + + + + +
Subtotal (95% CI)		**12399**		**8374**	**26.1%**	**1.42 [0.52 , 3.87]**	
Total events:	11		6				
Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 2 (P = 0.52); I² = 0%							
Test for overall effect: Z = 0.69 (P = 0.49)							
1.10.2 Medium-mortality countries							
RIX Li 2013b-CHN	0	25	0	25		Not estimable	+ + + + + +
RIX Li 2014-CHN	1	1666	1	1667	3.4%	1.00 [0.06 , 15.98]	+ + + + + +
RIX NCT00158756-RUS	1	161	0	48	2.6%	0.91 [0.04 , 21.92]	+ + + + + +
RIX Ruiz-Palac 06-LA/EU (2)	13	31673	20	31552	53.7%	0.65 [0.32 , 1.30]	+ + + + - +
RIX Salinas 2005-LA (3)	1	1618	0	537	2.6%	1.00 [0.04 , 24.44]	+ + + + - ?
RIX Tregnaghi 2011-LA (4)	4	4376	2	2192	9.1%	1.00 [0.18 , 5.47]	+ + + + + ?
Subtotal (95% CI)		**39519**		**36021**	**71.3%**	**0.72 [0.39 , 1.32]**	
Total events:	20		23				
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 4 (P = 0.99); I² = 0%							
Test for overall effect: Z = 1.07 (P = 0.28)							
1.10.3 High-mortality countries							
RIX Madhi 2010-AF (5)	1	3298	0	1641	2.6%	1.49 [0.06 , 36.63]	+ + + + + +
RIX Rivera 2011-DOM	0	100	0	100		Not estimable	+ + + + + +
RIX Steele 2008-ZAF	0	300	0	150		Not estimable	+ + ? + + +
RIX Steele 2010b-ZAF (5)	0	379	0	96		Not estimable	+ + + + + +
RIX Zaman 2017-BGD (6)	0	2307	0	2289		Not estimable	+ ? - ? - ?
Subtotal (95% CI)		**6384**		**4276**	**2.6%**	**1.49 [0.06 , 36.63]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.25 (P = 0.81)							
Total (95% CI)		**58302**		**48671**	**100.0%**	**0.87 [0.52 , 1.46]**	
Total events:	32		29				
Heterogeneity: Tau² = 0.00; Chi² = 3.09, df = 8 (P = 0.93); I² = 0%							
Test for overall effect: Z = 0.51 (P = 0.61)							
Test for subgroup differences: Chi² = 1.42, df = 2 (P = 0.49), I² = 0%							



Footnotes

(1) pre-term infants
(2) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Honduras, Nicaragua, Venezuela
(3) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela
(4) Multinational study: mainly medium-mortality countries (n=4) but also two high-mortality countries: Dominican Republic and Honduras
(5) 2 or 3 doses
(6) Adjusted for clustering: design effect of 2.53, villages randomised to Rotarix versus no intervention, true sample size: n=11,004

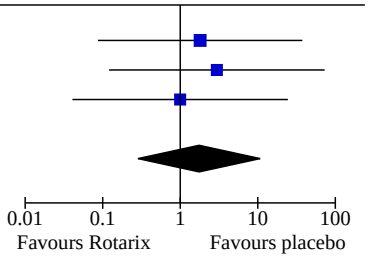
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.11. Comparison 1: Rotarix versus placebo, Outcome 11: Serious adverse events: Kawasaki disease

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
RIX Phua 2005-SGP	2	1811	0	653	35.7%	1.80 [0.09 , 37.54]
RIX Phua 2009-AS	1	4272	0	4226	32.1%	2.97 [0.12 , 72.83]
RIX Salinas 2005-LA	1	1618	0	537	32.2%	1.00 [0.04 , 24.44]
Total (95% CI)		**7701**		**5416**	**100.0%**	**1.75 [0.29 , 10.73]**
Total events:	4		0			

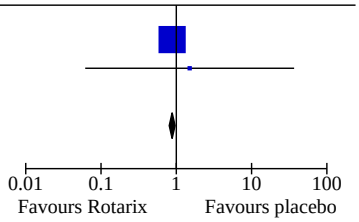
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Rotarix versus placebo, Outcome 12: Serious adverse events requiring hospitalization

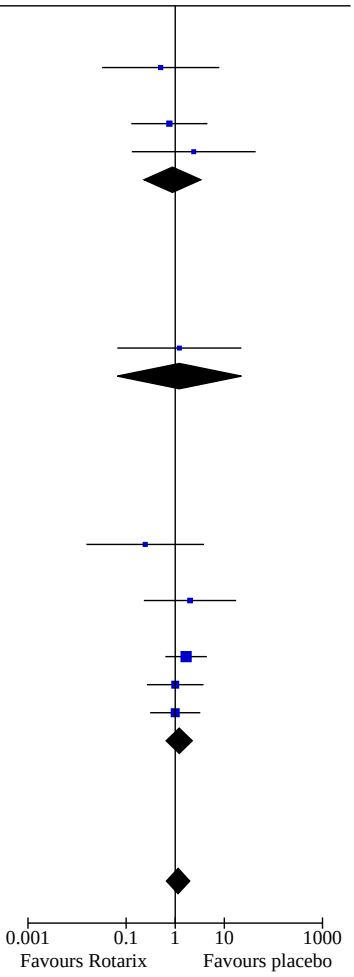
Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
RIX Ruiz-Palac 06-LA/EU	886	31673	1003	31552	99.9%	0.88 [0.81 , 0.96]
RIX Steele 2008-ZAF	1	300	0	150	0.1%	1.50 [0.06 , 36.72]
Total (95% CI)		**31973**		**31702**	**100.0%**	**0.88 [0.81 , 0.96]**
Total events:	887		1003			

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.81 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Rotarix versus placebo, Outcome 13: Rotavirus diarrhoea: of any severity (up to 2 months follow-up)

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Low-mortality countries						
RIX GSK[041] 2007-KOR	1	103	1	52	3.9%	0.50 [0.03 , 7.91]
RIX Kim 2012-KOR	0	508	0	176		Not estimable
RIX Omenaca 2012-EU (1)	3	670	2	339	9.3%	0.76 [0.13 , 4.52]
RIX Vesikari 2011-FIN	4	169	0	44	3.5%	2.38 [0.13 , 43.44]
Subtotal (95% CI)		**1450**		**611**	**16.7%**	**0.88 [0.23 , 3.32]**
Total events:	8		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.13.2 Medium-mortality countries						
RIX Kerdpanich 2010-THA	4	392	0	52	3.5%	1.21 [0.07 , 22.23]
Subtotal (95% CI)		**392**		**52**	**3.5%**	**1.21 [0.07 , 22.23]**
Total events:	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
1.13.3 High-mortality countries						
RIX Anh 2011-PHL	1	270	1	66	3.9%	0.24 [0.02 , 3.86]
RIX Anh 2011-VNM	0	275	0	71		Not estimable
RIX GSK[101555] 2008-PHL	4	100	1	50	6.3%	2.00 [0.23 , 17.43]
RIX Narang 2009-IND	0	182	0	181		Not estimable
RIX Rivera 2011-DOM	10	100	6	100	31.3%	1.67 [0.63 , 4.41]
RIX Steele 2010a-ZAF (2)	4	50	4	50	16.8%	1.00 [0.26 , 3.78]
RIX Zaman 2009-BGD	8	196	4	98	21.5%	1.00 [0.31 , 3.24]
Subtotal (95% CI)		**1173**		**616**	**79.7%**	**1.21 [0.65 , 2.22]**
Total events:	27		16			
Heterogeneity: Tau² = 0.00; Chi² = 2.10, df = 4 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		**3015**		**1279**	**100.0%**	**1.14 [0.66 , 1.97]**
Total events:	39		19			
Heterogeneity: Tau² = 0.00; Chi² = 2.92, df = 8 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 0.18, df = 2 (P = 0.91), I² = 0%						



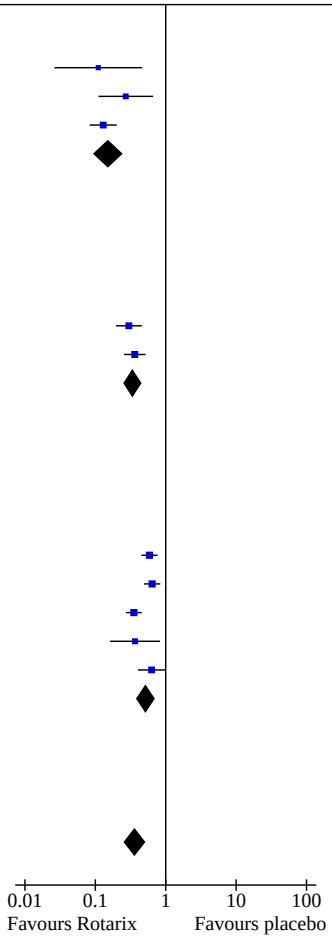
Footnotes

(1) pre-term infants

(2) HIV-positive infants receiving 3 doses

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

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Low-mortality countries						
RIX Bernstein 1999-USA	2	108	18	107	3.8%	0.11 [0.03 , 0.46]
RIX Vesikari 2004b-FIN	7	245	13	123	6.8%	0.27 [0.11 , 0.66]
RIX Vesikari 2007a-EU	24	2572	94	1302	10.9%	0.13 [0.08 , 0.20]
Subtotal (95% CI)		**2925**		**1532**	**21.5%**	**0.15 [0.10 , 0.24]**
Total events:	33		125			
Heterogeneity: Tau² = 0.03; Chi² = 2.29, df = 2 (P = 0.32); I² = 13%						
Test for overall effect: Z = 8.22 (P < 0.00001)						
1.14.2 Medium-mortality countries						
RIX Li 2014-CHN	27	1575	90	1573	11.1%	0.30 [0.20 , 0.46]
RIX Salinas 2005-LA (1)	59	1527	55	517	11.7%	0.36 [0.26 , 0.52]
Subtotal (95% CI)		**3102**		**2090**	**22.8%**	**0.34 [0.26 , 0.44]**
Total events:	86		145			
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 7.88 (P < 0.00001)						
1.14.3 High-mortality countries						
RIX Colgate 2016-BGD	67	350	114	350	12.5%	0.59 [0.45 , 0.76]
RIX Madhi 2010-MWI (2)	109	1182	85	591	12.5%	0.64 [0.49 , 0.84]
RIX Madhi 2010-ZAF (2)	91	2116	128	1050	12.5%	0.35 [0.27 , 0.46]
RIX Steele 2010b-ZAF (2)	13	379	9	96	7.4%	0.37 [0.16 , 0.83]
RIX Zaman 2017-BGD (3)	30	1816	53	2021	10.9%	0.63 [0.40 , 0.98]
Subtotal (95% CI)		**5843**		**4108**	**55.7%**	**0.51 [0.39 , 0.68]**
Total events:	310		389			
Heterogeneity: Tau² = 0.07; Chi² = 13.28, df = 4 (P = 0.010); I² = 70%						
Test for overall effect: Z = 4.64 (P < 0.00001)						
Total (95% CI)		**11870**		**7730**	**100.0%**	**0.36 [0.26 , 0.50]**
Total events:	429		659			
Heterogeneity: Tau² = 0.21; Chi² = 56.32, df = 9 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 6.10 (P < 0.00001)						
Test for subgroup differences: Chi² = 20.74, df = 2 (P < 0.0001), I² = 90.4%						



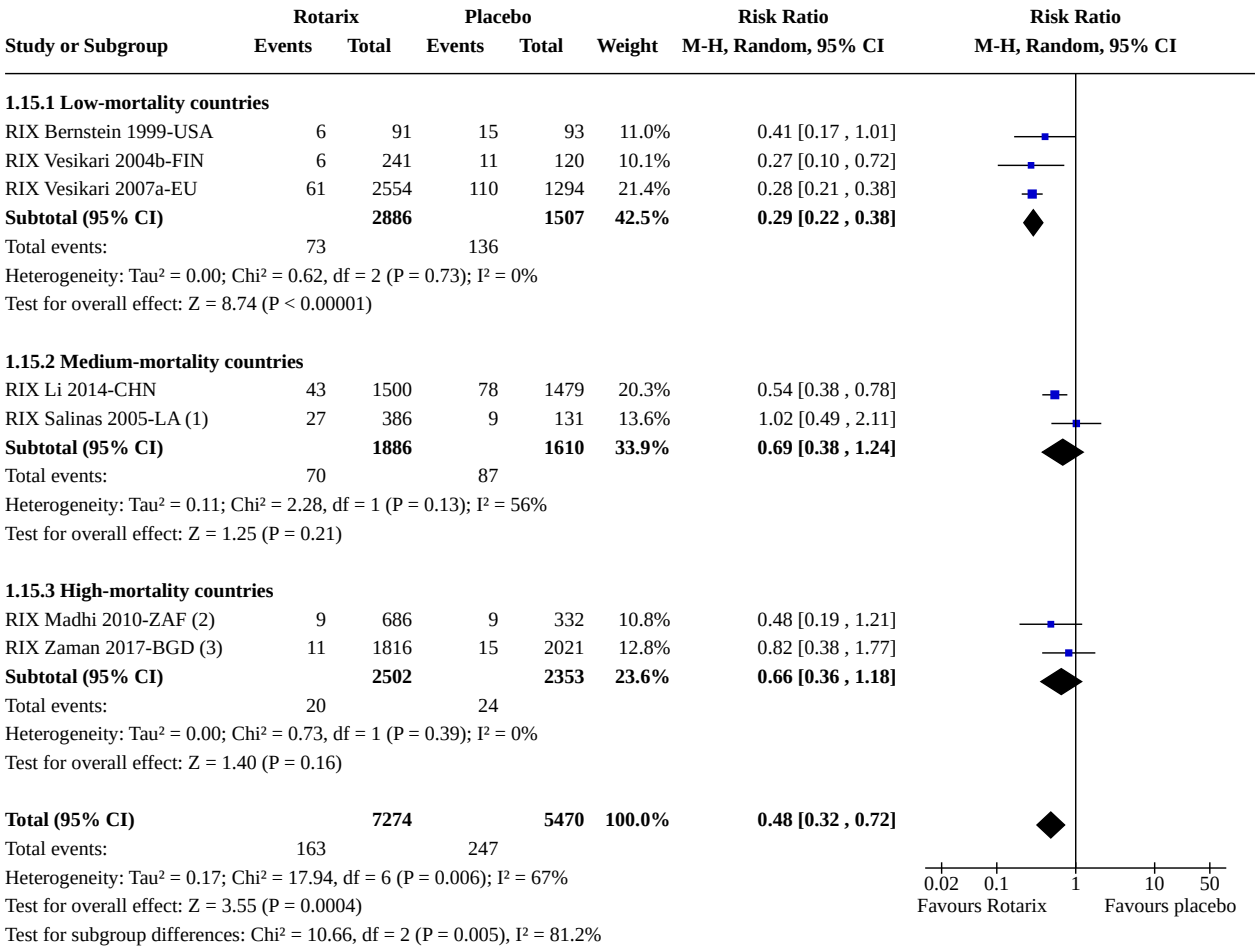
Footnotes

(1) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela

(2) 2 or 3 doses

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

Analysis 1.15. Comparison 1: Rotarix versus placebo, Outcome 15: Rotavirus diarrhoea: of any severity (2nd year of life)



Footnotes

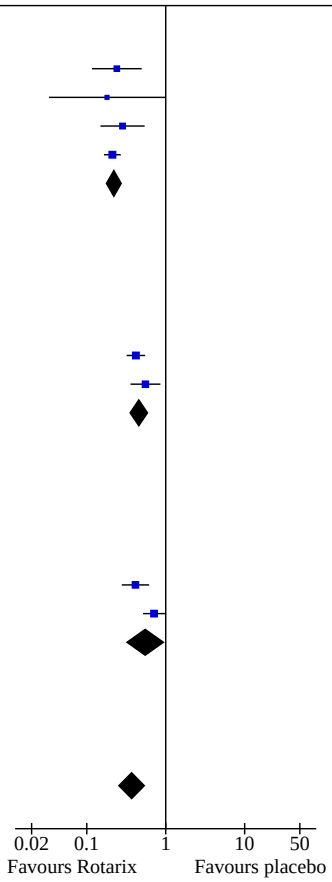
(1) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela

(2) 2 or 3 doses

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

Analysis 1.16. Comparison 1: Rotarix versus placebo, Outcome 16: Rotavirus diarrhoea: of any severity (up to 2 years follow-up)

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 Low-mortality countries						
RIX Bernstein 1999-USA	8	108	33	107	10.3%	0.24 [0.12 , 0.50]
RIX Phua 2005-SGP	2	1779	4	642	3.7%	0.18 [0.03 , 0.98]
RIX Vesikari 2004b-FIN	13	245	23	123	11.3%	0.28 [0.15 , 0.54]
RIX Vesikari 2007a-EU	85	2572	204	1302	15.9%	0.21 [0.17 , 0.27]
Subtotal (95% CI)		**4704**		**2174**	**41.2%**	**0.22 [0.18 , 0.27]**
Total events:	108		264			
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 3 (P = 0.84); I² = 0%						
Test for overall effect: Z = 13.74 (P < 0.00001)						
1.16.2 Medium-mortality countries						
RIX Li 2014-CHN	70	1575	167	1573	15.6%	0.42 [0.32 , 0.55]
RIX Salinas 2005-LA (1)	44	386	27	131	13.8%	0.55 [0.36 , 0.86]
Subtotal (95% CI)		**1961**		**1704**	**29.4%**	**0.46 [0.35 , 0.59]**
Total events:	114		194			
Heterogeneity: Tau² = 0.01; Chi² = 1.15, df = 1 (P = 0.28); I² = 13%						
Test for overall effect: Z = 6.06 (P < 0.00001)						
1.16.3 High-mortality countries						
RIX Madhi 2010-ZAF (2)	41	843	48	408	14.2%	0.41 [0.28 , 0.62]
RIX Zaman 2017-BGD (3)	65	2307	81	2042	15.1%	0.71 [0.52 , 0.98]
Subtotal (95% CI)		**3150**		**2450**	**29.4%**	**0.55 [0.32 , 0.93]**
Total events:	106		129			
Heterogeneity: Tau² = 0.11; Chi² = 4.30, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 2.21 (P = 0.03)						
Total (95% CI)		**9815**		**6328**	**100.0%**	**0.37 [0.25 , 0.54]**
Total events:	328		587			
Heterogeneity: Tau² = 0.21; Chi² = 43.31, df = 7 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 5.26 (P < 0.00001)						
Test for subgroup differences: Chi² = 22.97, df = 2 (P < 0.0001), I² = 91.3%						



Footnotes

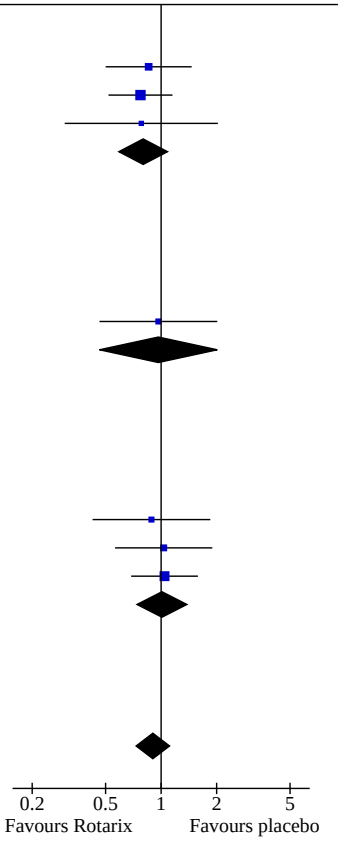
(1) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela

(2) 2 or 3 doses

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

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

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 Low-mortality countries						
RIX Kim 2012-KOR	42	508	17	176	15.1%	0.86 [0.50 , 1.46]
RIX Omenaca 2012-EU (1)	55	670	36	339	27.2%	0.77 [0.52 , 1.15]
RIX Vesikari 2011-FIN	15	169	5	44	4.8%	0.78 [0.30 , 2.03]
Subtotal (95% CI)		**1347**		**559**	**47.1%**	**0.80 [0.59 , 1.08]**
Total events:	112		58			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 2 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
1.17.2 Medium-mortality countries						
RIX Kerdpanich 2010-THA	51	392	7	52	8.0%	0.97 [0.46 , 2.02]
Subtotal (95% CI)		**392**		**52**	**8.0%**	**0.97 [0.46 , 2.02]**
Total events:	51		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
1.17.3 High-mortality countries						
RIX Anh 2011-PHL	29	270	8	66	8.0%	0.89 [0.42 , 1.85]
RIX Anh 2011-VNM	44	275	11	71	11.8%	1.03 [0.56 , 1.89]
RIX Steele 2010a-ZAF (2)	24	50	23	50	25.1%	1.04 [0.69 , 1.58]
Subtotal (95% CI)		**595**		**187**	**44.9%**	**1.01 [0.74 , 1.38]**
Total events:	97		42			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						
Total (95% CI)		**2334**		**798**	**100.0%**	**0.90 [0.73 , 1.11]**
Total events:	260		107			
Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 6 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 1.15, df = 2 (P = 0.56), I² = 0%						



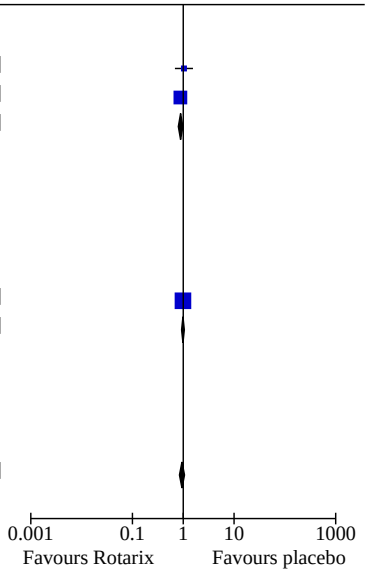
Footnotes

(1) pre-term infants

(2) HIV-positive infants receiving 3 doses

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

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Medium-mortality countries						
RIX Rivera 2011-DOM	32	100	31	100	6.8%	1.03 [0.69 , 1.55]
RIX Salinas 2005-LA (1)	656	1527	253	517	40.4%	0.88 [0.79 , 0.98]
Subtotal (95% CI)		**1627**		**617**	**47.3%**	**0.89 [0.80 , 0.98]**
Total events:	688		284			
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 2.31 (P = 0.02)						
1.18.2 High-mortality countries						
RIX Colgate 2016-BGD (2)	298	350	302	350	52.7%	0.99 [0.93 , 1.05]
Subtotal (95% CI)		**350**		**350**	**52.7%**	**0.99 [0.93 , 1.05]**
Total events:	298		302			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
Total (95% CI)		**1977**		**967**	**100.0%**	**0.94 [0.84 , 1.06]**
Total events:	986		586			
Heterogeneity: Tau² = 0.01; Chi² = 5.00, df = 2 (P = 0.08); I² = 60%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Chi² = 3.12, df = 1 (P = 0.08), I² = 67.9%						



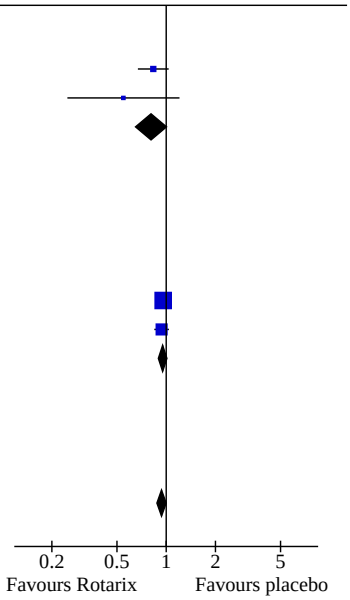
Footnotes

(1) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela

(2) no intervention control group

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

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 Low-mortality countries						
RIX Phua 2005-SGP	231	1779	100	642	8.6%	0.83 [0.67 , 1.04]
RIX Vesikari 2004b-FIN	12	245	11	123	0.7%	0.55 [0.25 , 1.21]
Subtotal (95% CI)		**2024**		**765**	**9.3%**	**0.81 [0.65 , 1.00]**
Total events:	243		111			
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%						
Test for overall effect: Z = 1.92 (P = 0.05)						
1.19.2 Medium-mortality countries						
RIX Li 2014-CHN	728	1575	759	1573	57.1%	0.96 [0.89 , 1.03]
RIX Salinas 2005-LA (1)	290	386	105	131	33.7%	0.94 [0.85 , 1.04]
Subtotal (95% CI)		**1961**		**1704**	**90.7%**	**0.95 [0.90 , 1.01]**
Total events:	1018		864			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.65 (P = 0.10)						
Total (95% CI)		**3985**		**2469**	**100.0%**	**0.94 [0.88 , 1.00]**
Total events:	1261		975			
Heterogeneity: Tau² = 0.00; Chi² = 3.30, df = 3 (P = 0.35); I² = 9%						
Test for overall effect: Z = 2.00 (P = 0.05)						
Test for subgroup differences: Chi² = 2.01, df = 1 (P = 0.16), I² = 50.2%						

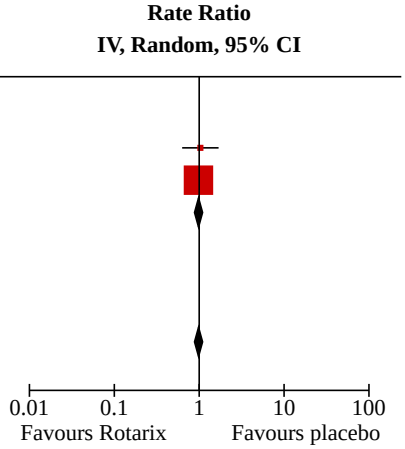


Footnotes

(1) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela

Analysis 1.20. Comparison 1: Rotarix versus placebo, Outcome 20: All-cause diarrhoea: all episodes (up to 1 year follow-up)

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
1.20.1 Medium-mortality countries				
RIX Rivera 2011-DOM	0.032	0.252	4.9%	1.03 [0.63 , 1.69]
RIX Salinas 2005-LA (1)	-0.02	0.057	95.1%	0.98 [0.88 , 1.10]
Subtotal (95% CI)			**100.0%**	**0.98 [0.88 , 1.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%				
Test for overall effect: Z = 0.31 (P = 0.75)				
Total (95% CI)			**100.0%**	**0.98 [0.88 , 1.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%				
Test for overall effect: Z = 0.31 (P = 0.75)				
Test for subgroup differences: Not applicable				

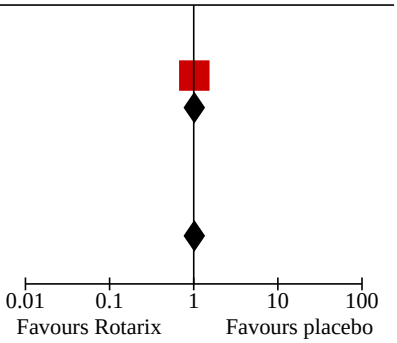


Footnotes

(1) Multinational study: mainly medium-mortality countries (n=2) but also one high-mortality country: Venezuela

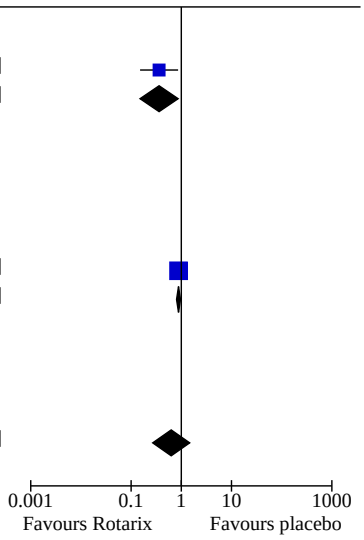
Analysis 1.21. Comparison 1: Rotarix versus placebo, Outcome 21: All-cause diarrhoea: all episodes (up to 2 years follow-up)

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
1.21.1 Low-mortality countries				
RIX Vesikari 2004b-FIN	0.016	0.137	100.0%	1.02 [0.78 , 1.33]
Subtotal (95% CI)			**100.0%**	**1.02 [0.78 , 1.33]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.12 (P = 0.91)				
Total (95% CI)			**100.0%**	**1.02 [0.78 , 1.33]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.12 (P = 0.91)				
Test for subgroup differences: Not applicable				



Analysis 1.22. Comparison 1: Rotarix versus placebo, Outcome 22: All-cause hospitalizations (up to 2 years follow-up)

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.22.1 Low-mortality countries						
RIX Phua 2005-SGP	10	1779	10	642	37.7%	0.36 [0.15 , 0.86]
Subtotal (95% CI)		**1779**		**642**	**37.7%**	**0.36 [0.15 , 0.86]**
Total events:	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.29 (P = 0.02)						
1.22.2 Medium-mortality countries						
RIX Ruiz-Palac 06-LA/EU (1)	886	31673	1003	31552	62.3%	0.88 [0.81 , 0.96]
Subtotal (95% CI)		**31673**		**31552**	**62.3%**	**0.88 [0.81 , 0.96]**
Total events:	886		1003			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.82 (P = 0.005)						
Total (95% CI)		**33452**		**32194**	**100.0%**	**0.63 [0.27 , 1.47]**
Total events:	896		1013			
Heterogeneity: Tau² = 0.30; Chi² = 3.97, df = 1 (P = 0.05); I² = 75%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Chi² = 3.97, df = 1 (P = 0.05), I² = 74.8%						

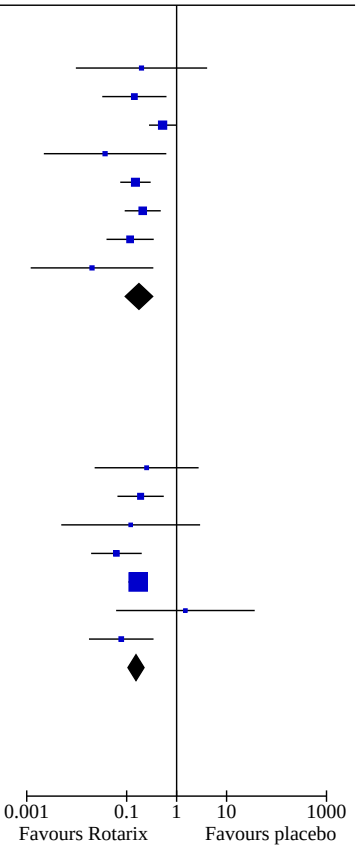


Footnotes

(1) Multinational study: mainly medium-mortality countries (n=7) but also 4 high-mortality countries: Dominican Republic, Honduras, Nicaragua, Venezuela

Analysis 1.23. Comparison 1: Rotarix versus placebo, Outcome 23: Rotavirus diarrhoea: requiring hospitalization

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.23.1 Up to 1 year follow-up (at least 1 rotavirus season)						
RIX Bernstein 1999-USA	0	108	2	107	3.8%	0.20 [0.01 , 4.08]
RIX Li 2014-CHN	2	1575	14	1573	11.0%	0.14 [0.03 , 0.63]
RIX Madhi 2010-AF (1)	20	3298	19	1641	21.9%	0.52 [0.28 , 0.98]
RIX Phua 2009-AS	0	5263	13	5256	4.2%	0.04 [0.00 , 0.62]
RIX Ruiz-Palac 06-LA/EU	9	9009	59	8858	20.8%	0.15 [0.07 , 0.30]
RIX Salinas 2005-LA	9	1392	14	454	18.8%	0.21 [0.09 , 0.48]
RIX Tregnaghi 2011-LA	4	4211	17	2099	15.3%	0.12 [0.04 , 0.35]
RIX Vesikari 2007a-EU	0	2572	12	1302	4.2%	0.02 [0.00 , 0.34]
Subtotal (95% CI)		**27428**		**21290**	**100.0%**	**0.18 [0.09 , 0.33]**
Total events:	44		150			
Heterogeneity: Tau² = 0.37; Chi² = 15.41, df = 7 (P = 0.03); I² = 55%						
Test for overall effect: Z = 5.40 (P < 0.00001)						
1.23.2 Up to 2 years follow-up (at least 2 rotavirus seasons)						
RIX Kawamura 2011-JPN	1	498	2	250	2.4%	0.25 [0.02 , 2.75]
RIX Li 2014-CHN	4	1575	21	1573	12.0%	0.19 [0.07 , 0.55]
RIX Phua 2005-SGP	0	1779	1	642	1.3%	0.12 [0.00 , 2.95]
RIX Phua 2009-AS	3	5263	48	5256	10.0%	0.06 [0.02 , 0.20]
RIX Ruiz-Palac 06-LA/EU	22	7205	127	7081	66.8%	0.17 [0.11 , 0.27]
RIX Vesikari 2004b-FIN	1	241	0	120	1.3%	1.50 [0.06 , 36.55]
RIX Vesikari 2007a-EU	2	2554	13	1294	6.2%	0.08 [0.02 , 0.34]
Subtotal (95% CI)		**19115**		**16216**	**100.0%**	**0.15 [0.11 , 0.22]**
Total events:	33		212			
Heterogeneity: Tau² = 0.00; Chi² = 5.66, df = 6 (P = 0.46); I² = 0%						
Test for overall effect: Z = 9.94 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%						

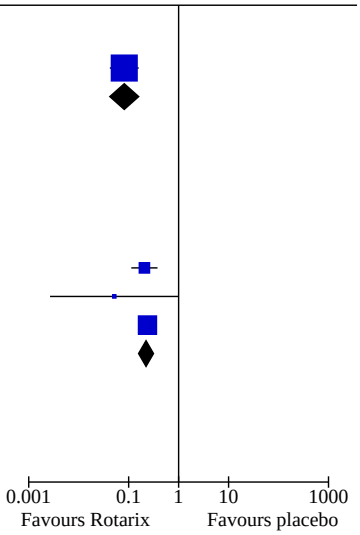


Footnotes

(1) 2 or 3 doses

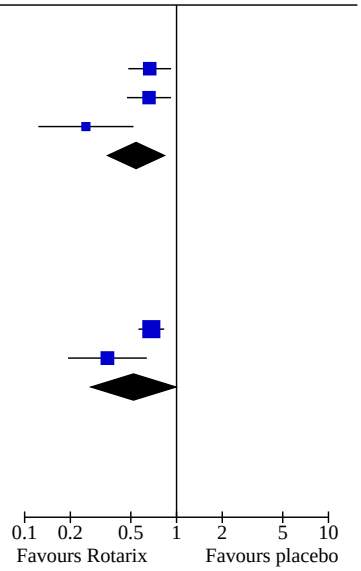
Analysis 1.24. Comparison 1: Rotarix versus placebo, Outcome 24: Rotavirus diarrhoea: requiring medical attention

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.24.1 Up to 1 year follow-up (at least 1 rotavirus season)						
RIX Vesikari 2007a-EU	10	2572	62	1302	100.0%	0.08 [0.04 , 0.16]
Subtotal (95% CI)		**2572**		**1302**	**100.0%**	**0.08 [0.04 , 0.16]**
Total events:	10		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.39 (P < 0.00001)						
1.24.2 Up to 2 years follow-up (at least 2 rotavirus seasons)						
RIX Kawamura 2011-JPN	14	498	34	250	32.3%	0.21 [0.11 , 0.38]
RIX Phua 2005-SGP	0	1779	3	642	1.3%	0.05 [0.00 , 1.00]
RIX Vesikari 2007a-EU	31	2554	66	1294	66.3%	0.24 [0.16 , 0.36]
Subtotal (95% CI)		**4831**		**2186**	**100.0%**	**0.22 [0.16 , 0.31]**
Total events:	45		103			
Heterogeneity: Tau² = 0.00; Chi² = 1.09, df = 2 (P = 0.58); I² = 0%						
Test for overall effect: Z = 8.57 (P < 0.00001)						

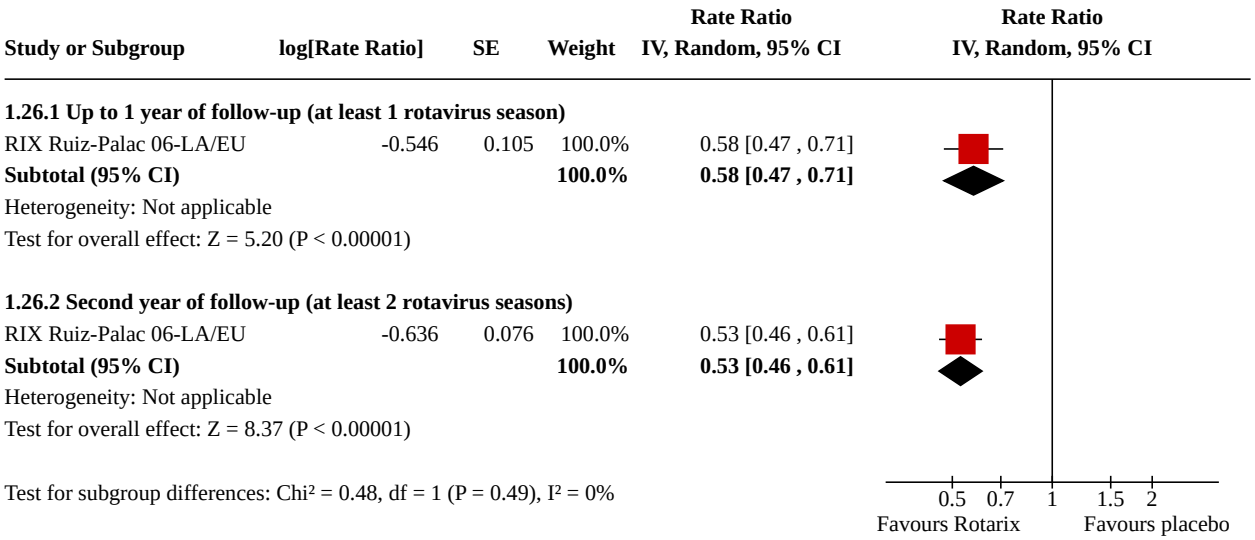


Analysis 1.25. Comparison 1: Rotarix versus placebo, Outcome 25: All-cause diarrhoea: cases requiring hospitalization

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.25.1 Up to one year of follow-up (at least 1 rotavirus season)						
RIX Phua 2009-AS	60	5263	90	5256	39.8%	0.67 [0.48 , 0.92]
RIX Tregnaghi 2011-LA	78	4211	59	2099	39.3%	0.66 [0.47 , 0.92]
RIX Vesikari 2007a-EU	11	2572	22	1302	20.9%	0.25 [0.12 , 0.52]
Subtotal (95% CI)		**12046**		**8657**	**100.0%**	**0.54 [0.35 , 0.83]**
Total events:	149		171			
Heterogeneity: Tau² = 0.09; Chi² = 6.20, df = 2 (P = 0.04); I² = 68%						
Test for overall effect: Z = 2.81 (P = 0.005)						
1.25.2 Second year of follow-up (at least 2 rotavirus seasons)						
RIX Phua 2009-AS	164	5263	240	5256	59.4%	0.68 [0.56 , 0.83]
RIX Vesikari 2007a-EU	18	2554	26	1294	40.6%	0.35 [0.19 , 0.64]
Subtotal (95% CI)		**7817**		**6550**	**100.0%**	**0.52 [0.27 , 0.99]**
Total events:	182		266			
Heterogeneity: Tau² = 0.17; Chi² = 4.31, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 2.00 (P = 0.05)						

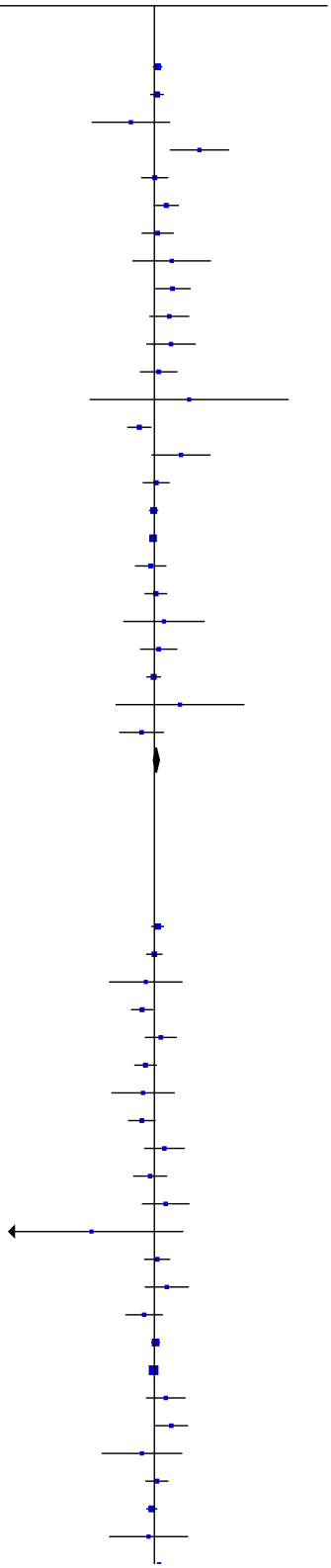


Analysis 1.26. Comparison 1: Rotarix versus placebo, Outcome 26: All-cause diarrhoea: episodes requiring hospitalization



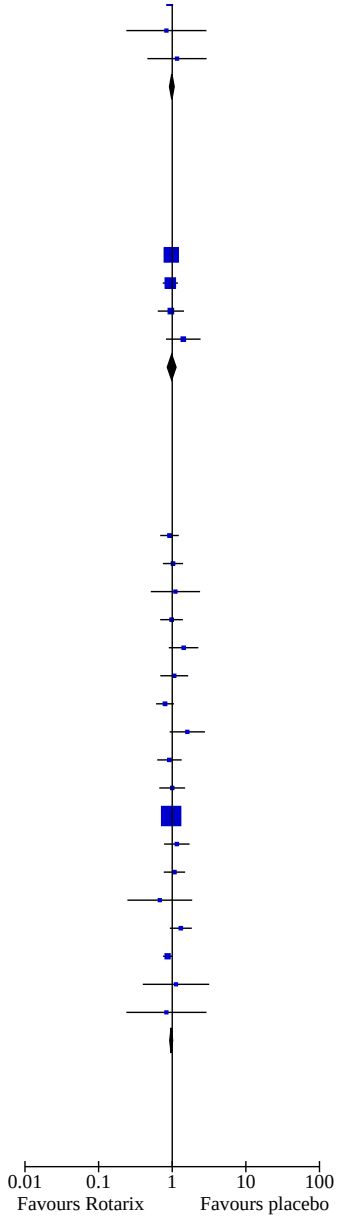
Analysis 1.27. Comparison 1: Rotarix versus placebo, Outcome 27: Reactogenicity: fever

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.27.1 After dose 1						
RIX Anh 2011-PHL	239	300	54	75	11.9%	1.11 [0.95 , 1.29]
RIX Anh 2011-VNM	182	297	44	78	9.1%	1.09 [0.88 , 1.35]
RIX Bernstein 1998-USA	3	21	6	20	0.6%	0.48 [0.14 , 1.65]
RIX Bernstein 1999-USA	21	108	5	107	1.0%	4.16 [1.63 , 10.63]
RIX Dennehy 2005-NA	83	421	21	108	3.8%	1.01 [0.66 , 1.56]
RIX GSK[021] 2007-PAN	91	177	18	51	4.3%	1.46 [0.98 , 2.17]
RIX GSK[033] 2007-LA	98	730	15	124	2.9%	1.11 [0.67 , 1.85]
RIX GSK[041] 2007-KOR	10	100	3	52	0.6%	1.73 [0.50 , 6.03]
RIX GSK[101555] 2008-PHL	39	100	11	50	2.3%	1.77 [1.00 , 3.16]
RIX Kawamura 2011-JPN	38	508	12	257	2.0%	1.60 [0.85 , 3.01]
RIX Kerdpanich 2010-THA	68	348	6	52	1.4%	1.69 [0.77 , 3.70]
RIX Kim 2012-KOR	43	508	13	176	2.2%	1.15 [0.63 , 2.08]
RIX Li 2013b-CHN	1	25	0	25	0.1%	3.00 [0.13 , 70.30]
RIX Li 2014-CHN	41	1513	66	1514	4.5%	0.62 [0.42 , 0.91]
RIX Narang 2009-IND	14	182	6	181	1.0%	2.32 [0.91 , 5.90]
RIX NCT00158756-RUS	43	78	13	25	3.8%	1.06 [0.69 , 1.62]
RIX Phua 2005-SGP	497	1811	183	653	12.3%	0.98 [0.85 , 1.13]
RIX Salinas 2005-LA	1002	1618	346	537	15.5%	0.96 [0.89 , 1.03]
RIX Steele 2008-ZAF	37	297	21	150	3.0%	0.89 [0.54 , 1.46]
RIX Steele 2010b-ZAF	62	189	30	96	4.9%	1.05 [0.73 , 1.50]
RIX Vesikari 2004a-FIN	8	122	3	62	0.5%	1.36 [0.37 , 4.93]
RIX Vesikari 2004b-FIN	32	265	14	133	2.2%	1.15 [0.63 , 2.07]
RIX Vesikari 2007a-EU	166	914	91	490	8.5%	0.98 [0.78 , 1.23]
RIX Vesikari 2011-FIN	9	200	1	50	0.2%	2.25 [0.29 , 17.35]
RIX Zaman 2009-BGD	16	196	12	98	1.6%	0.67 [0.33 , 1.35]
Subtotal (95% CI)		**11028**		**5164**	**100.0%**	**1.06 [0.97 , 1.17]**
Total events:	2843		994			
Heterogeneity: Tau² = 0.01; Chi² = 38.19, df = 24 (P = 0.03); I² = 37%						
Test for overall effect: Z = 1.30 (P = 0.20)						
1.27.2 After dose 2						
RIX Anh 2011-PHL	197	296	45	75	9.8%	1.11 [0.91 , 1.36]
RIX Anh 2011-VNM	141	286	36	73	6.5%	1.00 [0.77 , 1.30]
RIX Bernstein 1998-USA	4	21	5	20	0.4%	0.76 [0.24 , 2.44]
RIX Dennehy 2005-NA	82	394	31	101	3.9%	0.68 [0.48 , 0.96]
RIX GSK[021] 2007-PAN	57	168	13	47	1.9%	1.23 [0.74 , 2.04]
RIX GSK[033] 2007-LA	129	683	28	112	3.8%	0.76 [0.53 , 1.08]
RIX GSK[041] 2007-KOR	8	99	6	52	0.5%	0.70 [0.26 , 1.91]
RIX GSK[101555] 2008-PHL	29	98	22	50	2.6%	0.67 [0.43 , 1.04]
RIX Kawamura 2011-JPN	33	499	12	250	1.2%	1.38 [0.72 , 2.62]
RIX Kerdpanich 2010-THA	69	342	12	52	1.7%	0.87 [0.51 , 1.50]
RIX Kim 2012-KOR	33	508	8	176	0.9%	1.43 [0.67 , 3.03]
RIX Li 2013b-CHN	0	23	3	22	0.1%	0.14 [0.01 , 2.51]
RIX Li 2014-CHN	46	1449	42	1446	2.9%	1.09 [0.72 , 1.65]
RIX Narang 2009-IND	18	175	12	173	1.0%	1.48 [0.74 , 2.98]
RIX NCT00158756-RUS	22	76	10	25	1.4%	0.72 [0.40 , 1.31]
RIX Phua 2005-SGP	536	1779	186	642	16.2%	1.04 [0.90 , 1.20]
RIX Salinas 2005-LA	826	1534	288	522	25.1%	0.98 [0.89 , 1.07]
RIX Steele 2008-ZAF	34	282	12	143	1.3%	1.44 [0.77 , 2.69]
RIX Steele 2010b-ZAF	91	369	13	90	1.8%	1.71 [1.00 , 2.91]
RIX Vesikari 2004a-FIN	5	111	4	60	0.3%	0.68 [0.19 , 2.42]
RIX Vesikari 2004b-FIN	69	255	31	124	3.6%	1.08 [0.75 , 1.56]
RIX Vesikari 2007a-EU	244	905	142	486	12.1%	0.92 [0.77 , 1.10]
RIX Vesikari 2011-FIN	10	196	3	49	0.3%	0.83 [0.24 , 2.91]
RIX Zaman 2009-BGD	14	195	6	97	0.6%	1.16 [0.46 , 2.93]



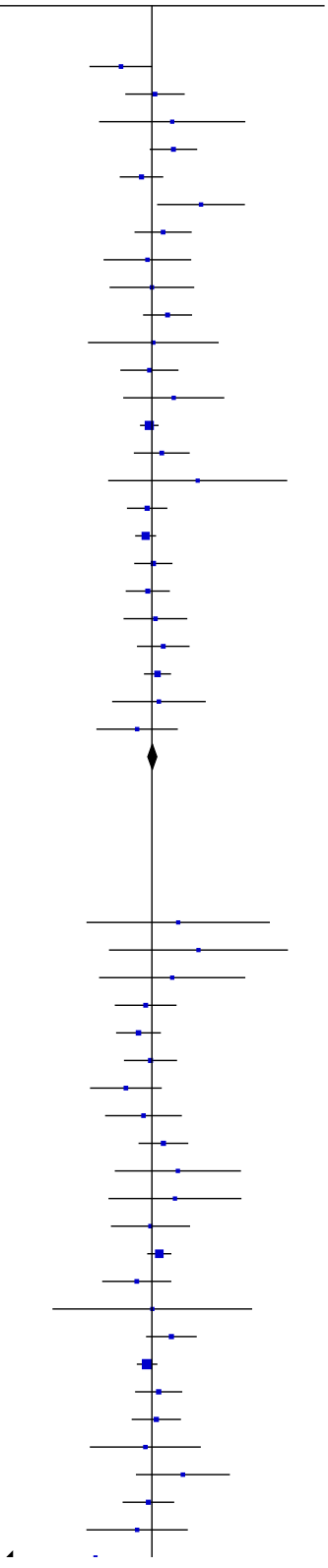
Analysis 1.27. (Continued)

RIX Vesikari 2011-FIN	10	196	3	49	0.3%	0.83 [0.24 , 2.91]
RIX Zaman 2009-BGD	14	195	6	97	0.6%	1.16 [0.46 , 2.93]
Subtotal (95% CI)		**10743**		**4887**	**100.0%**	**0.99 [0.92 , 1.06]**
Total events:	2697		970			
Heterogeneity: Tau² = 0.00; Chi² = 26.11, df = 23 (P = 0.30); I² = 12%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.27.3 After dose 3						
RIX Anh 2011-PHL	182	293	48	75	50.0%	0.97 [0.80 , 1.18]
RIX Anh 2011-VNM	146	283	40	73	32.8%	0.94 [0.74 , 1.19]
RIX GSK[021] 2007-PAN	63	168	18	46	10.9%	0.96 [0.64 , 1.44]
RIX Steele 2010b-ZAF	76	364	13	88	6.3%	1.41 [0.82 , 2.43]
Subtotal (95% CI)		**1108**		**282**	**100.0%**	**0.98 [0.86 , 1.13]**
Total events:	467		119			
Heterogeneity: Tau² = 0.00; Chi² = 2.03, df = 3 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.80)						
1.27.4 End of follow-up						
RIX Dennehy 2005-NA	136	421	38	108	2.2%	0.92 [0.69 , 1.23]
RIX GSK[033] 2007-LA	199	730	33	124	1.9%	1.02 [0.75 , 1.40]
RIX GSK[041] 2007-KOR	17	100	8	52	0.3%	1.10 [0.51 , 2.39]
RIX GSK[101555] 2008-PHL	47	100	24	50	1.5%	0.98 [0.69 , 1.40]
RIX Kawamura 2011-JPN	62	508	22	257	0.9%	1.43 [0.90 , 2.26]
RIX Kerdpanich 2010-THA	114	348	16	52	1.0%	1.06 [0.69 , 1.64]
RIX Li 2014-CHN	83	1513	104	1514	2.4%	0.80 [0.60 , 1.06]
RIX Narang 2009-IND	29	182	18	181	0.6%	1.60 [0.92 , 2.78]
RIX Omenaca 2012-EU	54	203	29	100	1.3%	0.92 [0.63 , 1.34]
RIX Rivera 2011-DOM	32	100	32	100	1.2%	1.00 [0.67 , 1.50]
RIX Salinas 2005-LA	1238	1618	425	537	72.4%	0.97 [0.92 , 1.02]
RIX Steele 2008-ZAF	64	297	28	150	1.2%	1.15 [0.78 , 1.72]
RIX Steele 2010a-ZAF	30	50	28	50	1.7%	1.07 [0.77 , 1.50]
RIX Vesikari 2004a-FIN	8	122	6	62	0.2%	0.68 [0.25 , 1.87]
RIX Vesikari 2004b-FIN	86	265	33	133	1.6%	1.31 [0.93 , 1.84]
RIX Vesikari 2007a-EU	310	914	192	490	9.3%	0.87 [0.75 , 1.00]
RIX Vesikari 2011-FIN	18	200	4	50	0.2%	1.13 [0.40 , 3.18]
RIX Zaman 2009-BGD	10	196	3	49	0.1%	0.83 [0.24 , 2.91]
Subtotal (95% CI)		**7867**		**4059**	**100.0%**	**0.97 [0.93 , 1.01]**
Total events:	2537		1043			
Heterogeneity: Tau² = 0.00; Chi² = 15.47, df = 17 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.47 (P = 0.14)						



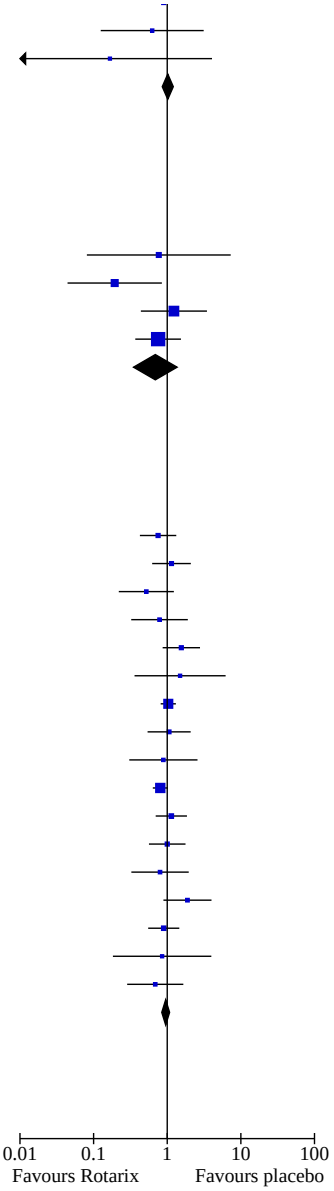
Analysis 1.28. Comparison 1: Rotarix versus placebo, Outcome 28: Reactogenicity: diarrhoea

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.28.1 After dose 1						
RIX Anh 2011-PHL	9	300	6	75	2.0%	0.38 [0.14 , 1.02]
RIX Anh 2011-VNM	21	297	5	78	2.2%	1.10 [0.43 , 2.83]
RIX Bernstein 1998-USA	2	21	1	20	0.4%	1.90 [0.19 , 19.40]
RIX Bernstein 1999-USA	18	108	9	107	3.5%	1.98 [0.93 , 4.21]
RIX Dennehy 2005-NA	28	421	10	108	4.2%	0.72 [0.36 , 1.43]
RIX GSK[021] 2007-PAN	33	177	2	51	1.0%	4.75 [1.18 , 19.14]
RIX GSK[033] 2007-LA	42	730	5	124	2.4%	1.43 [0.58 , 3.54]
RIX GSK[041] 2007-KOR	5	100	3	52	1.0%	0.87 [0.22 , 3.49]
RIX GSK[101555] 2008-PHL	6	100	3	50	1.1%	1.00 [0.26 , 3.83]
RIX Kawamura 2011-JPN	26	508	8	257	3.3%	1.64 [0.76 , 3.58]
RIX Kerdpanich 2010-THA	7	348	1	52	0.5%	1.05 [0.13 , 8.33]
RIX Kim 2012-KOR	16	508	6	176	2.3%	0.92 [0.37 , 2.32]
RIX Li 2013b-CHN	4	25	2	25	0.8%	2.00 [0.40 , 9.95]
RIX Li 2014-CHN	80	1513	87	1514	22.8%	0.92 [0.68 , 1.24]
RIX Narang 2009-IND	11	182	8	181	2.5%	1.37 [0.56 , 3.32]
RIX NCT00158756-RUS	6	78	0	25	0.2%	4.28 [0.25 , 73.38]
RIX Phua 2005-SGP	31	1811	13	653	4.8%	0.86 [0.45 , 1.63]
RIX Salinas 2005-LA	111	1618	45	537	18.0%	0.82 [0.59 , 1.14]
RIX Steele 2008-ZAF	29	297	14	150	5.4%	1.05 [0.57 , 1.92]
RIX Steele 2010b-ZAF	19	189	11	96	4.0%	0.88 [0.44 , 1.77]
RIX Vesikari 2004a-FIN	11	122	5	62	1.9%	1.12 [0.41 , 3.08]
RIX Vesikari 2004b-FIN	20	265	7	133	2.8%	1.43 [0.62 , 3.31]
RIX Vesikari 2007a-EU	68	2613	29	1331	10.7%	1.19 [0.78 , 1.84]
RIX Vesikari 2011-FIN	10	200	2	50	0.9%	1.25 [0.28 , 5.53]
RIX Zaman 2009-BGD	5	196	4	98	1.2%	0.63 [0.17 , 2.28]
Subtotal (95% CI)		**12727**		**6005**	**100.0%**	**1.01 [0.88 , 1.17]**
Total events:	618		286			
Heterogeneity: Tau² = 0.00; Chi² = 21.56, df = 24 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.86)						
1.28.2 After dose 2						
RIX Anh 2011-PHL	4	296	0	75	0.3%	2.30 [0.13 , 42.31]
RIX Anh 2011-VNM	8	286	0	73	0.4%	4.38 [0.26 , 75.08]
RIX Bernstein 1998-USA	2	21	1	20	0.5%	1.90 [0.19 , 19.40]
RIX Dennehy 2005-NA	16	394	5	101	3.1%	0.82 [0.31 , 2.19]
RIX GSK[021] 2007-PAN	21	168	9	47	5.9%	0.65 [0.32 , 1.33]
RIX GSK[033] 2007-LA	35	683	6	112	4.2%	0.96 [0.41 , 2.22]
RIX GSK[041] 2007-KOR	5	99	6	52	2.3%	0.44 [0.14 , 1.37]
RIX GSK[101555] 2008-PHL	6	98	4	50	2.0%	0.77 [0.23 , 2.59]
RIX Kawamura 2011-JPN	23	499	8	250	4.7%	1.44 [0.65 , 3.17]
RIX Kerdpanich 2010-THA	15	342	1	52	0.7%	2.28 [0.31 , 16.90]
RIX Kim 2012-KOR	6	508	1	176	0.7%	2.08 [0.25 , 17.15]
RIX Li 2013b-CHN	4	23	4	22	1.9%	0.96 [0.27 , 3.36]
RIX Li 2014-CHN	57	1449	45	1446	20.1%	1.26 [0.86 , 1.86]
RIX Narang 2009-IND	5	175	8	173	2.5%	0.62 [0.21 , 1.85]
RIX NCT00158756-RUS	1	76	0	25	0.3%	1.01 [0.04 , 24.11]
RIX Phua 2005-SGP	36	1779	7	642	4.6%	1.86 [0.83 , 4.15]
RIX Salinas 2005-LA	116	1534	46	522	27.7%	0.86 [0.62 , 1.19]
RIX Steele 2008-ZAF	22	282	9	143	5.3%	1.24 [0.59 , 2.62]
RIX Steele 2010b-ZAF	33	369	7	90	4.8%	1.15 [0.53 , 2.51]
RIX Vesikari 2004a-FIN	3	111	2	60	1.0%	0.81 [0.14 , 4.72]
RIX Vesikari 2004b-FIN	11	255	2	124	1.3%	2.67 [0.60 , 11.88]
RIX Vesikari 2007a-EU	15	905	9	486	4.4%	0.90 [0.39 , 2.03]
RIX Vesikari 2011-FIN	5	196	2	49	1.1%	0.63 [0.12 , 3.13]
RIX Zaman 2009-BGD	0	195	1	97	0.3%	0.17 [0.01 , 4.05]



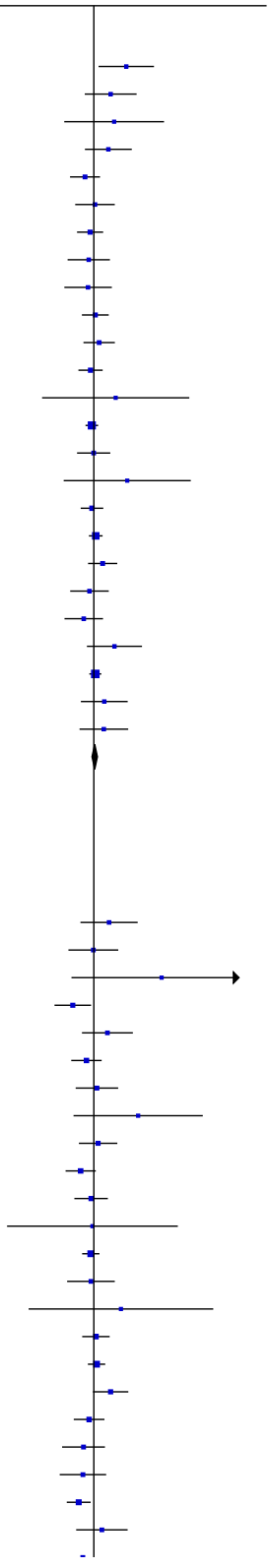
Analysis 1.28. (Continued)

RIX Vesikari 2011-FIN	5	196	2	49	1.1%	0.63 [0.12 , 3.13]
RIX Zaman 2009-BGD	0	195	1	97	0.3%	0.17 [0.01 , 4.05]
Subtotal (95% CI)		**10743**		**4887**	**100.0%**	**1.02 [0.86 , 1.21]**
Total events:	449		183			
Heterogeneity: Tau² = 0.00; Chi² = 16.52, df = 23 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.28.3 After dose 3						
RIX Anh 2011-PHL	3	293	1	75	8.3%	0.77 [0.08 , 7.28]
RIX Anh 2011-VNM	3	283	4	73	17.2%	0.19 [0.04 , 0.85]
RIX GSK[021] 2007-PAN	18	168	4	46	29.3%	1.23 [0.44 , 3.46]
RIX Steele 2010b-ZAF	28	364	9	88	45.2%	0.75 [0.37 , 1.54]
Subtotal (95% CI)		**1108**		**282**	**100.0%**	**0.69 [0.35 , 1.36]**
Total events:	52		18			
Heterogeneity: Tau² = 0.13; Chi² = 4.11, df = 3 (P = 0.25); I² = 27%						
Test for overall effect: Z = 1.07 (P = 0.28)						
1.28.4 End of follow-up						
RIX Dennehy 2005-NA	41	421	14	108	4.6%	0.75 [0.43 , 1.33]
RIX GSK[033] 2007-LA	74	730	11	124	4.1%	1.14 [0.62 , 2.09]
RIX GSK[041] 2007-KOR	9	100	9	52	2.0%	0.52 [0.22 , 1.23]
RIX GSK[101555] 2008-PHL	11	100	7	50	1.9%	0.79 [0.32 , 1.90]
RIX Kawamura 2011-JPN	43	508	14	257	4.4%	1.55 [0.87 , 2.79]
RIX Kerdpanich 2010-THA	20	348	2	52	0.7%	1.49 [0.36 , 6.21]
RIX Li 2014-CHN	127	1513	123	1514	26.3%	1.03 [0.81 , 1.31]
RIX Narang 2009-IND	16	182	15	181	3.3%	1.06 [0.54 , 2.08]
RIX Omenaca 2012-EU	9	203	5	100	1.3%	0.89 [0.31 , 2.58]
RIX Salinas 2005-LA	206	1618	85	537	27.4%	0.80 [0.64 , 1.02]
RIX Steele 2008-ZAF	45	297	20	150	6.2%	1.14 [0.70 , 1.85]
RIX Steele 2010a-ZAF	16	50	16	50	4.5%	1.00 [0.56 , 1.77]
RIX Vesikari 2004a-FIN	11	122	7	62	1.8%	0.80 [0.33 , 1.96]
RIX Vesikari 2004b-FIN	30	265	8	133	2.6%	1.88 [0.89 , 3.99]
RIX Vesikari 2007a-EU	44	2613	25	1331	6.3%	0.90 [0.55 , 1.46]
RIX Vesikari 2011-FIN	7	193	2	47	0.6%	0.85 [0.18 , 3.97]
RIX Zaman 2009-BGD	11	196	8	98	1.9%	0.69 [0.29 , 1.65]
Subtotal (95% CI)		**9459**		**4846**	**100.0%**	**0.95 [0.84 , 1.08]**
Total events:	720		371			
Heterogeneity: Tau² = 0.00; Chi² = 13.27, df = 16 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.44)						



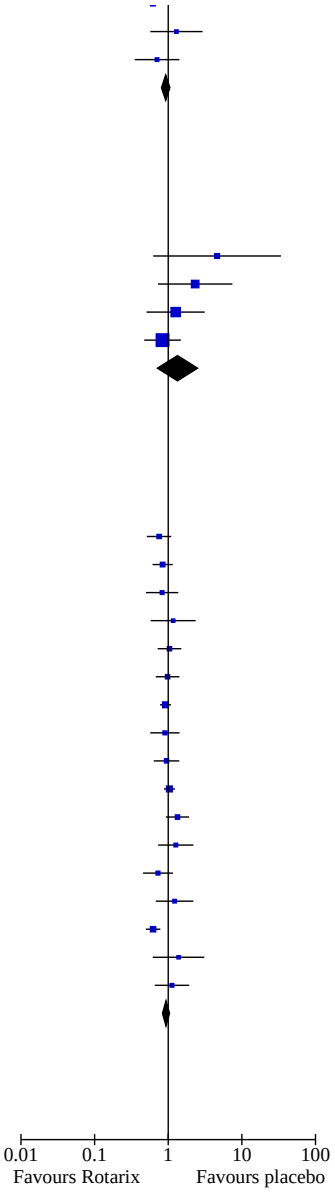
Analysis 1.29. Comparison 1: Rotarix versus placebo, Outcome 29: Reactogenicity: vomiting

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.29.1 After dose 1						
RIX Anh 2011-PHL	56	300	5	75	0.9%	2.80 [1.16 , 6.74]
RIX Anh 2011-VNM	39	297	6	78	1.1%	1.71 [0.75 , 3.89]
RIX Bernstein 1998-USA	4	21	2	20	0.3%	1.90 [0.39 , 9.28]
RIX Bernstein 1999-USA	16	108	10	107	1.3%	1.59 [0.75 , 3.33]
RIX Dennehy 2005-NA	56	421	19	108	3.2%	0.76 [0.47 , 1.22]
RIX GSK[021] 2007-PAN	36	177	10	51	1.8%	1.04 [0.55 , 1.94]
RIX GSK[033] 2007-LA	115	730	22	124	4.2%	0.89 [0.59 , 1.34]
RIX GSK[041] 2007-KOR	18	100	11	52	1.6%	0.85 [0.43 , 1.66]
RIX GSK[101555] 2008-PHL	15	100	9	50	1.3%	0.83 [0.39 , 1.77]
RIX Kawamura 2011-JPN	58	508	28	257	4.0%	1.05 [0.68 , 1.60]
RIX Kerdpanich 2010-THA	103	348	13	52	2.9%	1.18 [0.72 , 1.95]
RIX Kim 2012-KOR	78	508	30	176	4.9%	0.90 [0.61 , 1.32]
RIX Li 2013b-CHN	2	25	1	25	0.1%	2.00 [0.19 , 20.67]
RIX Li 2014-CHN	165	1513	176	1514	18.0%	0.94 [0.77 , 1.15]
RIX Narang 2009-IND	24	182	24	181	2.6%	0.99 [0.59 , 1.68]
RIX NCT00158756-RUS	9	78	1	25	0.2%	2.88 [0.38 , 21.66]
RIX Phua 2005-SGP	102	1811	39	653	5.6%	0.94 [0.66 , 1.35]
RIX Salinas 2005-LA	285	1618	89	537	15.3%	1.06 [0.86 , 1.32]
RIX Steele 2008-ZAF	55	297	21	150	3.4%	1.32 [0.83 , 2.10]
RIX Steele 2010b-ZAF	24	189	14	96	1.9%	0.87 [0.47 , 1.61]
RIX Vesikari 2004a-FIN	20	122	14	62	1.9%	0.73 [0.39 , 1.34]
RIX Vesikari 2004b-FIN	23	265	6	133	0.9%	1.92 [0.80 , 4.61]
RIX Vesikari 2007a-EU	290	2613	141	1331	20.0%	1.05 [0.87 , 1.27]
RIX Vesikari 2011-FIN	39	200	7	50	1.3%	1.39 [0.66 , 2.93]
RIX Zaman 2009-BGD	22	196	8	98	1.2%	1.38 [0.64 , 2.98]
Subtotal (95% CI)		**12727**		**6005**	**100.0%**	**1.03 [0.94 , 1.12]**
Total events:	1654		706			
Heterogeneity: Tau² = 0.00; Chi² = 20.22, df = 24 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
1.29.2 After dose 2						
RIX Anh 2011-PHL	32	296	5	75	2.0%	1.62 [0.65 , 4.02]
RIX Anh 2011-VNM	27	286	7	73	2.5%	0.98 [0.45 , 2.17]
RIX Bernstein 1998-USA	4	21	0	20	0.2%	8.59 [0.49 , 150.00]
RIX Dennehy 2005-NA	30	394	15	101	4.3%	0.51 [0.29 , 0.92]
RIX GSK[021] 2007-PAN	33	168	6	47	2.4%	1.54 [0.69 , 3.45]
RIX GSK[033] 2007-LA	82	683	17	112	5.8%	0.79 [0.49 , 1.28]
RIX GSK[041] 2007-KOR	21	99	10	52	3.3%	1.10 [0.56 , 2.16]
RIX GSK[101555] 2008-PHL	8	98	1	50	0.4%	4.08 [0.53 , 31.73]
RIX Kawamura 2011-JPN	32	499	14	250	4.0%	1.15 [0.62 , 2.11]
RIX Kerdpanich 2010-THA	65	342	15	52	5.8%	0.66 [0.41 , 1.06]
RIX Kim 2012-KOR	45	508	17	176	5.0%	0.92 [0.54 , 1.56]
RIX Li 2013b-CHN	1	23	1	22	0.2%	0.96 [0.06 , 14.37]
RIX Li 2014-CHN	91	1449	100	1446	12.1%	0.91 [0.69 , 1.19]
RIX Narang 2009-IND	12	175	13	173	2.7%	0.91 [0.43 , 1.94]
RIX NCT00158756-RUS	3	76	0	25	0.2%	2.36 [0.13 , 44.25]
RIX Phua 2005-SGP	77	1779	26	642	6.8%	1.07 [0.69 , 1.65]
RIX Salinas 2005-LA	189	1534	59	522	12.1%	1.09 [0.83 , 1.43]
RIX Steele 2008-ZAF	47	282	14	143	4.5%	1.70 [0.97 , 2.99]
RIX Steele 2010b-ZAF	60	369	17	90	5.7%	0.86 [0.53 , 1.40]
RIX Vesikari 2004a-FIN	16	111	12	60	3.3%	0.72 [0.37 , 1.42]
RIX Vesikari 2004b-FIN	16	255	11	124	2.8%	0.71 [0.34 , 1.48]
RIX Vesikari 2007a-EU	53	905	46	486	8.2%	0.62 [0.42 , 0.90]
RIX Vesikari 2011-FIN	31	196	6	49	2.4%	1.29 [0.57 , 2.92]
RIX Zaman 2009-BGD	17	195	12	97	3.1%	0.70 [0.35 , 1.42]



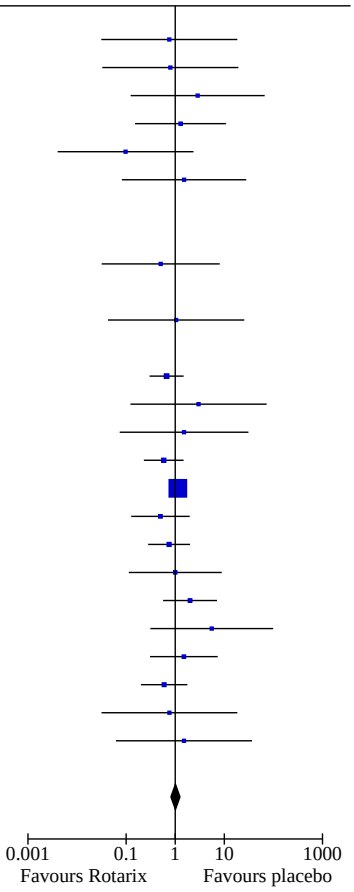
Analysis 1.29. (Continued)

RIX Vesikari 2011-FIN	31	196	6	49	2.4%	1.29 [0.57 , 2.92]
RIX Zaman 2009-BGD	17	195	12	97	3.1%	0.70 [0.35 , 1.42]
Subtotal (95% CI)		**10743**		**4887**	**100.0%**	**0.92 [0.81 , 1.05]**
Total events:	992		424			
Heterogeneity: Tau² = 0.02; Chi² = 28.02, df = 23 (P = 0.21); I² = 18%						
Test for overall effect: Z = 1.18 (P = 0.24)						
1.29.3 After dose 3						
RIX Anh 2011-PHL	18	293	1	75	8.6%	4.61 [0.63 , 33.96]
RIX Anh 2011-VNM	27	283	3	73	20.3%	2.32 [0.72 , 7.44]
RIX GSK[021] 2007-PAN	23	168	5	46	27.9%	1.26 [0.51 , 3.13]
RIX Steele 2010b-ZAF	45	364	13	88	43.3%	0.84 [0.47 , 1.48]
Subtotal (95% CI)		**1108**		**282**	**100.0%**	**1.34 [0.71 , 2.50]**
Total events:	113		22			
Heterogeneity: Tau² = 0.15; Chi² = 4.79, df = 3 (P = 0.19); I² = 37%						
Test for overall effect: Z = 0.90 (P = 0.37)						
1.29.4 End of follow-up						
RIX Dennehy 2005-NA	79	421	27	108	5.8%	0.75 [0.51 , 1.10]
RIX GSK[033] 2007-LA	168	730	34	124	7.4%	0.84 [0.61 , 1.15]
RIX GSK[041] 2007-KOR	27	100	17	52	3.8%	0.83 [0.50 , 1.37]
RIX GSK[101555] 2008-PHL	21	100	9	50	2.2%	1.17 [0.58 , 2.36]
RIX Kawamura 2011-JPN	74	508	36	257	6.1%	1.04 [0.72 , 1.50]
RIX Kerdpanich 2010-THA	131	348	20	52	6.1%	0.98 [0.68 , 1.42]
RIX Li 2014-CHN	213	1513	232	1514	13.2%	0.92 [0.77 , 1.09]
RIX Narang 2009-IND	29	182	32	181	4.4%	0.90 [0.57 , 1.43]
RIX Omenaca 2012-EU	52	203	27	100	5.5%	0.95 [0.64 , 1.41]
RIX Salinas 2005-LA	403	1618	129	537	13.1%	1.04 [0.87 , 1.23]
RIX Steele 2008-ZAF	82	297	31	150	6.2%	1.34 [0.93 , 1.92]
RIX Steele 2010a-ZAF	19	50	15	50	3.3%	1.27 [0.73 , 2.20]
RIX Vesikari 2004a-FIN	30	122	21	62	4.3%	0.73 [0.46 , 1.16]
RIX Vesikari 2004b-FIN	34	265	14	133	3.0%	1.22 [0.68 , 2.19]
RIX Vesikari 2007a-EU	154	2613	126	1331	10.7%	0.62 [0.50 , 0.78]
RIX Vesikari 2011-FIN	34	193	6	47	1.7%	1.38 [0.62 , 3.09]
RIX Zaman 2009-BGD	36	196	16	98	3.4%	1.13 [0.66 , 1.92]
Subtotal (95% CI)		**9459**		**4846**	**100.0%**	**0.93 [0.84 , 1.04]**
Total events:	1586		792			
Heterogeneity: Tau² = 0.02; Chi² = 24.61, df = 16 (P = 0.08); I² = 35%						
Test for overall effect: Z = 1.24 (P = 0.21)						



Analysis 1.30. Comparison 1: Rotarix versus placebo, Outcome 30: Adverse events requiring discontinuation (end of follow-up)

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
RIX Anh 2011-PHL	1	300	0	75	0.4%	0.76 [0.03 , 18.41]
RIX Anh 2011-VNM	1	297	0	78	0.4%	0.80 [0.03 , 19.34]
RIX Bernstein 1998-USA	1	21	0	20	0.5%	2.86 [0.12 , 66.44]
RIX Dennehy 2005-NA	5	421	1	108	1.0%	1.28 [0.15 , 10.86]
RIX GSK[021] 2007-PAN	0	177	1	51	0.4%	0.10 [0.00 , 2.35]
RIX GSK[033] 2007-LA	4	730	0	122	0.5%	1.51 [0.08 , 27.95]
RIX GSK[041] 2007-KOR	0	103	0	52		Not estimable
RIX GSK[101555] 2008-PHL	0	100	0	50		Not estimable
RIX Kawamura 2011-JPN	1	508	1	257	0.6%	0.51 [0.03 , 8.06]
RIX Kerdpanich 2010-THA	0	348	0	52		Not estimable
RIX Kim 2012-KOR	1	508	0	176	0.4%	1.04 [0.04 , 25.49]
RIX Li 2013b-CHN	0	25	0	25		Not estimable
RIX Li 2014-CHN	10	1666	15	1667	7.1%	0.67 [0.30 , 1.48]
RIX Narang 2009-IND	1	182	0	181	0.4%	2.98 [0.12 , 72.76]
RIX NCT00158756-RUS	2	161	0	48	0.5%	1.51 [0.07 , 30.97]
RIX Phua 2009-AS	7	5263	12	5256	5.2%	0.58 [0.23 , 1.48]
RIX Ruiz-Palac 06-LA/EU	118	31673	104	31552	64.8%	1.13 [0.87 , 1.47]
RIX Steele 2008-ZAF	4	300	4	150	2.4%	0.50 [0.13 , 1.97]
RIX Steele 2010a-ZAF	6	50	8	50	4.6%	0.75 [0.28 , 2.00]
RIX Steele 2010b-ZAF	4	379	1	95	0.9%	1.00 [0.11 , 8.87]
RIX Tregnaghi 2011-LA	12	4376	3	2192	2.8%	2.00 [0.57 , 7.09]
RIX Vesikari 2004a-FIN	5	128	0	64	0.5%	5.54 [0.31 , 98.71]
RIX Vesikari 2004b-FIN	6	270	2	135	1.8%	1.50 [0.31 , 7.33]
RIX Vesikari 2007a-EU	7	2646	6	1348	3.8%	0.59 [0.20 , 1.77]
RIX Vesikari 2011-FIN	1	200	0	50	0.4%	0.76 [0.03 , 18.41]
RIX Zaman 2009-BGD	1	196	0	98	0.4%	1.51 [0.06 , 36.67]
Total (95% CI)		**51028**		**43952**	**100.0%**	**1.01 [0.82 , 1.25]**
Total events:	198		158			



Heterogeneity: Tau² = 0.00; Chi² = 11.59, df = 21 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable

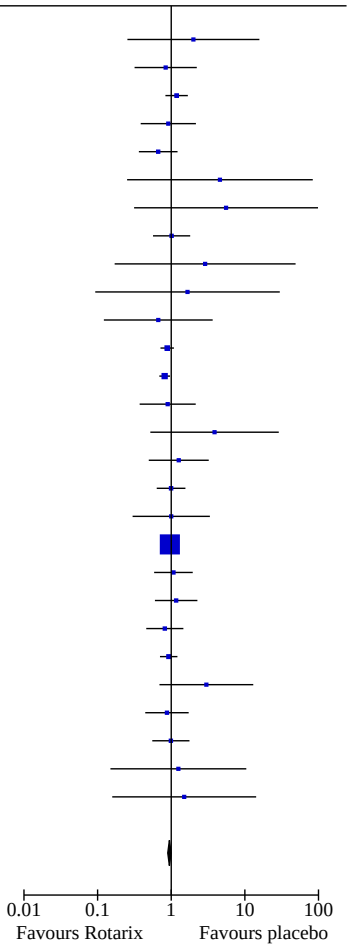
Analysis 1.31. Comparison 1: Rotarix versus placebo, Outcome 31: Dropouts before the end of the trial

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
RIX Anh 2011-PHL	8	300	1	75	0.1%	2.00 [0.25 , 15.75]
RIX Anh 2011-VNM	16	297	5	78	0.3%	0.84 [0.32 , 2.22]
RIX Colgate 2016-BGD	58	350	49	350	2.1%	1.18 [0.83 , 1.68]
RIX GSK[021] 2007-PAN	19	177	6	51	0.3%	0.91 [0.38 , 2.16]
RIX GSK[033] 2007-LA	47	730	12	124	0.7%	0.67 [0.36 , 1.22]
RIX GSK[041] 2007-KOR	4	103	0	52	0.0%	4.59 [0.25 , 83.60]
RIX GSK[101555] 2008-PHL	5	100	0	50	0.0%	5.55 [0.31 , 98.50]
RIX Kawamura 2011-JPN	32	508	16	257	0.8%	1.01 [0.57 , 1.81]
RIX Kerdpanich 2010-THA	9	348	0	52	0.0%	2.89 [0.17 , 48.85]
RIX Kim 2012-KOR	5	508	0	76	0.0%	1.66 [0.09 , 29.80]
RIX Li 2013b-CHN	2	25	3	25	0.1%	0.67 [0.12 , 3.65]
RIX Li 2014-CHN	148	1666	168	1667	5.9%	0.88 [0.71 , 1.09]
RIX Madhi 2010-AF	324	3298	198	1641	9.4%	0.81 [0.69 , 0.96]
RIX Narang 2009-IND	9	182	10	181	0.3%	0.90 [0.37 , 2.15]
RIX NCT00158756-RUS	13	161	1	48	0.1%	3.88 [0.52 , 28.88]
RIX Omenaca 2012-EU	15	670	6	339	0.3%	1.26 [0.50 , 3.23]
RIX Phua 2005-SGP	69	1811	25	653	1.3%	1.00 [0.64 , 1.56]
RIX Rivera 2011-DOM	5	100	5	100	0.2%	1.00 [0.30 , 3.35]
RIX Ruiz-Palac 06-LA/EU	1920	31673	1997	31552	70.9%	0.96 [0.90 , 1.02]
RIX Steele 2008-ZAF	30	300	14	150	0.7%	1.07 [0.59 , 1.96]
RIX Steele 2010a-ZAF	14	50	12	50	0.6%	1.17 [0.60 , 2.27]
RIX Steele 2010b-ZAF	42	379	13	96	0.8%	0.82 [0.46 , 1.46]
RIX Tregnaghi 2011-LA	142	4376	77	2192	3.5%	0.92 [0.70 , 1.21]
RIX Vesikari 2004a-FIN	12	128	2	64	0.1%	3.00 [0.69 , 13.00]
RIX Vesikari 2004b-FIN	21	270	12	135	0.6%	0.88 [0.44 , 1.72]
RIX Vesikari 2007a-EU	33	2646	17	1348	0.8%	0.99 [0.55 , 1.77]
RIX Vesikari 2011-FIN	5	200	1	50	0.1%	1.25 [0.15 , 10.46]
RIX Zaman 2009-BGD	3	196	1	98	0.1%	1.50 [0.16 , 14.23]
Total (95% CI)		**51552**		**41554**	**100.0%**	**0.94 [0.90 , 0.99]**
Total events:	3010		2651			

Heterogeneity: Tau² = 0.00; Chi² = 16.56, df = 27 (P = 0.94); I² = 0%

Test for overall effect: Z = 2.18 (P = 0.03)

Test for subgroup differences: Not applicable

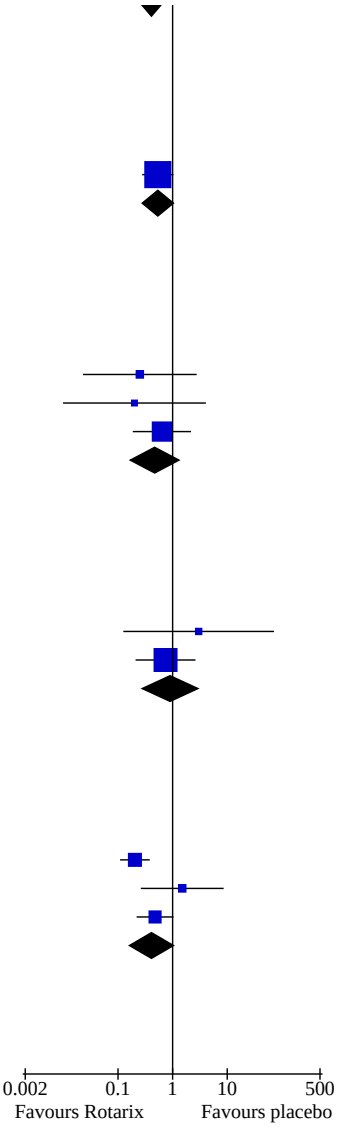


Analysis 1.32. Comparison 1: Rotarix versus placebo, Outcome 32: Subgroup analysis: rotavirus diarrhoea of any severity (by G- or P-type)

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.32.1 G1						
RIX Kawamura 2011-JPN	5	498	19	250	14.1%	0.13 [0.05 , 0.35]
RIX Li 2014-CHN	22	1575	47	1573	18.3%	0.47 [0.28 , 0.77]
RIX Ruiz-Palac 06-LA/EU	3	9009	36	8858	12.3%	0.08 [0.03 , 0.27]
RIX Salinas 2005-LA	26	1527	31	517	18.3%	0.28 [0.17 , 0.47]
RIX Steele 2010a-ZAF	2	50	0	50	3.8%	5.00 [0.25 , 101.58]
RIX Vesikari 2007a-EU	18	2572	89	1302	18.3%	0.10 [0.06 , 0.17]
RIX Zaman 2017-BGD (1)	7	1816	15	2021	14.8%	0.52 [0.21 , 1.27]
Subtotal (95% CI)		**17047**		**14571**	**100.0%**	**0.24 [0.13 , 0.47]**
Total events:	83		237			
Heterogeneity: Tau² = 0.54; Chi² = 29.97, df = 6 (P < 0.0001); I² = 80%						
Test for overall effect: Z = 4.26 (P < 0.0001)						
1.32.2 G2						
RIX Kawamura 2011-JPN	1	498	2	250	1.4%	0.25 [0.02 , 2.75]
RIX Li 2014-CHN	42	1575	102	1573	66.1%	0.41 [0.29 , 0.59]
RIX Ruiz-Palac 06-LA/EU	6	9009	10	8858	8.0%	0.59 [0.21 , 1.62]
RIX Salinas 2005-LA	1	1527	3	517	1.6%	0.11 [0.01 , 1.08]
RIX Steele 2010a-ZAF	0	50	1	50	0.8%	0.33 [0.01 , 7.99]
RIX Vesikari 2007a-EU	14	2572	17	1302	16.6%	0.42 [0.21 , 0.84]
RIX Zaman 2017-BGD (1)	4	1816	7	2021	5.5%	0.64 [0.19 , 2.17]
Subtotal (95% CI)		**17047**		**14571**	**100.0%**	**0.42 [0.32 , 0.56]**
Total events:	68		142			
Heterogeneity: Tau² = 0.00; Chi² = 2.38, df = 6 (P = 0.88); I² = 0%						
Test for overall effect: Z = 5.90 (P < 0.00001)						
1.32.3 G3						
RIX Kawamura 2011-JPN	3	498	13	250	39.2%	0.12 [0.03 , 0.40]
RIX Li 2014-CHN	0	1575	11	1573	7.6%	0.04 [0.00 , 0.74]
RIX Salinas 2005-LA	1	1527	2	517	10.6%	0.17 [0.02 , 1.86]
RIX Steele 2010a-ZAF	0	50	1	50	6.0%	0.33 [0.01 , 7.99]
RIX Vesikari 2007a-EU	3	2572	10	1302	36.6%	0.15 [0.04 , 0.55]
Subtotal (95% CI)		**6222**		**3692**	**100.0%**	**0.13 [0.06 , 0.29]**
Total events:	7		37			
Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 4 (P = 0.89); I² = 0%						
Test for overall effect: Z = 5.09 (P < 0.00001)						
1.32.4 G4						
RIX Kawamura 2011-JPN	1	498	1	250	9.3%	0.50 [0.03 , 7.99]
RIX Salinas 2005-LA	1	1527	0	517	7.0%	1.02 [0.04 , 24.93]
RIX Vesikari 2007a-EU	6	2572	18	1302	83.8%	0.17 [0.07 , 0.42]
Subtotal (95% CI)		**4597**		**2069**	**100.0%**	**0.21 [0.09 , 0.49]**
Total events:	8		19			
Heterogeneity: Tau² = 0.00; Chi² = 1.53, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 3.61 (P = 0.0003)						
1.32.5 G9						
RIX Kawamura 2011-JPN	5	498	5	250	11.3%	0.50 [0.15 , 1.72]
RIX Li 2014-CHN	1	1575	5	1573	4.3%	0.20 [0.02 , 1.71]
RIX Salinas 2005-LA	29	1527	19	517	30.2%	0.52 [0.29 , 0.91]
RIX Vesikari 2007a-EU	38	2572	71	1302	39.9%	0.27 [0.18 , 0.40]
RIX Zaman 2017-BGD (1)	6	1816	8	2021	14.3%	0.83 [0.29 , 2.40]
Subtotal (95% CI)		**7988**		**5663**	**100.0%**	**0.41 [0.26 , 0.65]**
Total events:	79		108			
Heterogeneity: Tau² = 0.10; Chi² = 6.61, df = 4 (P = 0.16); I² = 39%						

Analysis 1.32. (Continued)

Total events:	79		108			
Heterogeneity: Tau² = 0.10; Chi² = 6.61, df = 4 (P = 0.16); I² = 39%						
Test for overall effect: Z = 3.77 (P = 0.0002)						
1.32.6 G12						
RIX Zaman 2017-BGD (1)	13	1816	27	2021	100.0%	0.54 [0.28 , 1.04]
Subtotal (95% CI)		**1816**		**2021**	**100.0%**	**0.54 [0.28 , 1.04]**
Total events:	13		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
1.32.7 P4						
RIX Kawamura 2011-JPN	1	498	2	250	18.4%	0.25 [0.02 , 2.75]
RIX Steele 2010a-ZAF	0	50	2	50	11.6%	0.20 [0.01 , 4.06]
RIX Zaman 2017-BGD	4	1816	7	2021	70.0%	0.64 [0.19 , 2.17]
Subtotal (95% CI)		**2364**		**2321**	**100.0%**	**0.47 [0.17 , 1.31]**
Total events:	5		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 2 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.45 (P = 0.15)						
1.32.8 P6						
RIX Steele 2010a-ZAF	1	50	0	50	13.7%	3.00 [0.13 , 71.92]
RIX Zaman 2017-BGD (1)	4	1816	6	2021	86.3%	0.74 [0.21 , 2.62]
Subtotal (95% CI)		**1866**		**2071**	**100.0%**	**0.90 [0.28 , 2.90]**
Total events:	5		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.86)						
1.32.9 P8						
RIX Kawamura 2011-JPN	13	498	32	250	42.8%	0.20 [0.11 , 0.38]
RIX Steele 2010a-ZAF	3	50	2	50	18.5%	1.50 [0.26 , 8.60]
RIX Zaman 2017-BGD (1)	9	1816	21	2021	38.7%	0.48 [0.22 , 1.04]
Subtotal (95% CI)		**2364**		**2321**	**100.0%**	**0.41 [0.16 , 1.04]**
Total events:	25		55			
Heterogeneity: Tau² = 0.42; Chi² = 6.01, df = 2 (P = 0.05); I² = 67%						
Test for overall effect: Z = 1.88 (P = 0.06)						
Test for subgroup differences: Chi² = 14.65, df = 8 (P = 0.07), I² = 45.4%						



Footnotes

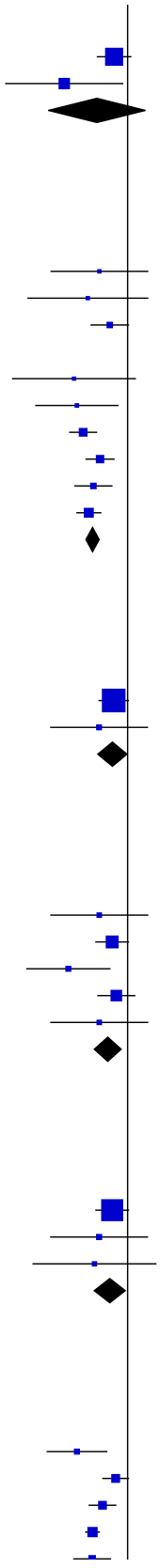
(1) Adjusted for clustering: design effect of 2.53, villages randomised to Rotarix versus no intervention

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

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.33.1 G1						
RIX Kawamura 2011-JPN	1	498	6	250	5.7%	0.08 [0.01 , 0.69]
RIX Li 2014-CHN	9	1575	25	1573	15.3%	0.36 [0.17 , 0.77]
RIX Madhi 2010-MWI	6	1030	5	483	11.3%	0.56 [0.17 , 1.83]
RIX Madhi 2010-ZAF	11	1944	18	960	15.4%	0.30 [0.14 , 0.64]
RIX Phua 2009-AS	0	5263	21	5256	3.7%	0.02 [0.00 , 0.38]
RIX Ruiz-Palac 06-LA/EU	13	10159	70	10010	16.9%	0.18 [0.10 , 0.33]
RIX Salinas 2005-LA	14	1527	18	517	16.0%	0.26 [0.13 , 0.53]
RIX Tregnaghi 2011-LA	0	4211	1	2099	3.0%	0.17 [0.01 , 4.08]
RIX Vesikari 2007a-EU	4	2572	57	1302	12.8%	0.04 [0.01 , 0.10]
Subtotal (95% CI)		**28779**		**22450**	**100.0%**	**0.19 [0.10 , 0.34]**
Total events:	58		221			
Heterogeneity: Tau² = 0.45; Chi² = 23.13, df = 8 (P = 0.003); I² = 65%						
Test for overall effect: Z = 5.50 (P < 0.00001)						
1.33.2 G2						
RIX Li 2014-CHN	11	1575	40	1573	47.3%	0.27 [0.14 , 0.53]
RIX Madhi 2010-MWI	2	1030	1	483	3.6%	0.94 [0.09 , 10.32]
RIX Madhi 2010-ZAF	1	1944	6	960	4.7%	0.08 [0.01 , 0.68]
RIX Phua 2005-SGP	0	1779	1	642	2.0%	0.12 [0.00 , 2.95]
RIX Phua 2009-AS	0	5263	2	5256	2.3%	0.20 [0.01 , 4.16]
RIX Ruiz-Palac 06-LA/EU	7	10159	12	10010	24.0%	0.57 [0.23 , 1.46]
RIX Salinas 2005-LA	1	1618	3	537	4.1%	0.11 [0.01 , 1.06]
RIX Tregnaghi 2011-LA	1	4211	2	2099	3.6%	0.25 [0.02 , 2.75]
RIX Vesikari 2007a-EU	2	2572	7	1302	8.4%	0.14 [0.03 , 0.70]
Subtotal (95% CI)		**30151**		**22862**	**100.0%**	**0.29 [0.18 , 0.45]**
Total events:	25		74			
Heterogeneity: Tau² = 0.00; Chi² = 6.21, df = 8 (P = 0.62); I² = 0%						
Test for overall effect: Z = 5.35 (P < 0.00001)						
1.33.3 G3						
RIX Kawamura 2011-JPN	0	498	4	250	4.8%	0.06 [0.00 , 1.03]
RIX Li 2014-CHN	0	1575	3	1573	4.7%	0.14 [0.01 , 2.76]
RIX Madhi 2010-MWI	0	1030	0	483		Not estimable
RIX Madhi 2010-ZAF	2	1944	6	960	16.0%	0.16 [0.03 , 0.81]
RIX Phua 2005-SGP	2	1779	0	642	4.4%	1.81 [0.09 , 37.57]
RIX Phua 2009-AS	1	5263	18	5256	10.1%	0.06 [0.01 , 0.42]
RIX Ruiz-Palac 06-LA/EU	6	10159	23	10010	50.6%	0.26 [0.10 , 0.63]
RIX Vesikari 2007a-EU	1	2572	8	1302	9.5%	0.06 [0.01 , 0.51]
Subtotal (95% CI)		**24820**		**20476**	**100.0%**	**0.18 [0.09 , 0.34]**
Total events:	12		62			
Heterogeneity: Tau² = 0.00; Chi² = 5.87, df = 6 (P = 0.44); I² = 0%						
Test for overall effect: Z = 5.31 (P < 0.00001)						
1.33.4 G4						
RIX Phua 2005-SGP	0	1779	1	642	16.7%	0.12 [0.00 , 2.95]
RIX Ruiz-Palac 06-LA/EU	8	10159	20	10010	53.7%	0.39 [0.17 , 0.89]
RIX Vesikari 2007a-EU	1	2572	11	1302	29.6%	0.05 [0.01 , 0.36]
Subtotal (95% CI)		**14510**		**11954**	**100.0%**	**0.17 [0.04 , 0.78]**
Total events:	9		32			
Heterogeneity: Tau² = 0.95; Chi² = 4.09, df = 2 (P = 0.13); I² = 51%						
Test for overall effect: Z = 2.27 (P = 0.02)						
1.33.5 G8						
RIX Madhi 2010-MWI	11	1030	10	483	65.4%	0.52 [0.22 , 1.21]

Analysis 1.33. (Continued)

1.33.5 G8						
RIX Madhi 2010-MWI	11	1030	10	483	65.4%	0.52 [0.22 , 1.21]
RIX Madhi 2010-ZAF	0	1944	5	960	34.6%	0.04 [0.00 , 0.81]
Subtotal (95% CI)		**2974**		**1443**	**100.0%**	**0.22 [0.02 , 2.37]**
Total events:	11		15			
Heterogeneity: Tau² = 2.05; Chi² = 2.73, df = 1 (P = 0.10); I² = 63%						
Test for overall effect: Z = 1.25 (P = 0.21)						
1.33.6 G9						
RIX Kawamura 2011-JPN	1	498	2	250	1.8%	0.25 [0.02 , 2.75]
RIX Li 2014-CHN	0	1575	3	1573	1.2%	0.14 [0.01 , 2.76]
RIX Madhi 2010-MWI	8	1030	9	483	11.6%	0.42 [0.16 , 1.07]
RIX Madhi 2010-ZAF	0	1944	0	960		Not estimable
RIX Phua 2005-SGP	0	1779	2	642	1.1%	0.07 [0.00 , 1.50]
RIX Phua 2009-AS	1	5263	12	5256	2.5%	0.08 [0.01 , 0.64]
RIX Ruiz-Palac 06-LA/EU	9	10159	79	10100	21.9%	0.11 [0.06 , 0.23]
RIX Salinas 2005-LA	13	1527	17	517	20.4%	0.26 [0.13 , 0.53]
RIX Tregnaghi 2011-LA	6	4211	16	2099	11.9%	0.19 [0.07 , 0.48]
RIX Vesikari 2007a-EU	13	2572	44	1302	27.5%	0.15 [0.08 , 0.28]
Subtotal (95% CI)		**30558**		**23182**	**100.0%**	**0.18 [0.13 , 0.25]**
Total events:	51		184			
Heterogeneity: Tau² = 0.00; Chi² = 7.41, df = 8 (P = 0.49); I² = 0%						
Test for overall effect: Z = 10.43 (P < 0.00001)						
1.33.7 G12						
RIX Madhi 2010-MWI	14	1030	13	483	91.2%	0.51 [0.24 , 1.07]
RIX Madhi 2010-ZAF	1	1944	2	960	8.8%	0.25 [0.02 , 2.72]
Subtotal (95% CI)		**2974**		**1443**	**100.0%**	**0.47 [0.23 , 0.97]**
Total events:	15		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 2.05 (P = 0.04)						
1.33.8 P4						
RIX Anh 2011-PHL	1	4211	2	2099	7.0%	0.25 [0.02 , 2.75]
RIX Madhi 2010-MWI	11	1030	11	483	41.4%	0.47 [0.20 , 1.07]
RIX Madhi 2010-ZAF	1	1944	9	960	9.3%	0.05 [0.01 , 0.43]
RIX Ruiz-Palac 06-LA/EU	7	10159	12	10010	35.2%	0.57 [0.23 , 1.46]
RIX Tregnaghi 2011-LA	1	4211	2	2099	7.0%	0.25 [0.02 , 2.75]
Subtotal (95% CI)		**21555**		**15651**	**100.0%**	**0.38 [0.20 , 0.73]**
Total events:	21		36			
Heterogeneity: Tau² = 0.09; Chi² = 4.74, df = 4 (P = 0.32); I² = 16%						
Test for overall effect: Z = 2.91 (P = 0.004)						
1.33.9 P6						
RIX Madhi 2010-MWI	11	1030	11	483	83.8%	0.47 [0.20 , 1.07]
RIX Madhi 2010-ZAF	1	1944	2	960	10.0%	0.25 [0.02 , 2.72]
RIX Ruiz-Palac 06-LA/EU	0	10159	2	10010	6.2%	0.20 [0.01 , 4.10]
Subtotal (95% CI)		**13133**		**11453**	**100.0%**	**0.42 [0.20 , 0.89]**
Total events:	12		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 2.26 (P = 0.02)						
1.33.10 P8						
RIX Kawamura 2011-JPN	2	498	12	250	9.5%	0.08 [0.02 , 0.37]
RIX Madhi 2010-MWI	19	1030	16	483	22.5%	0.56 [0.29 , 1.07]
RIX Madhi 2010-ZAF	13	1944	22	960	21.9%	0.29 [0.15 , 0.58]
RIX Ruiz-Palac 06-LA/EU	34	10159	187	10010	29.1%	0.18 [0.12 , 0.26]
RIX Tregnaghi 2011-LA	6	4211	17	2099	16.9%	0.18 [0.07 , 0.45]

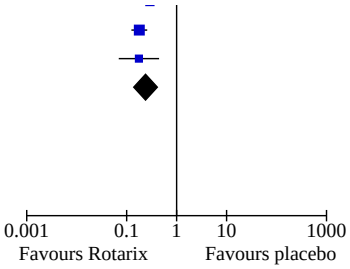


Analysis 1.33. (Continued)

RIX Ruiz-Palac 06-LA/EU	34	10159	187	10010	29.1%	0.18 [0.12 , 0.26]
RIX Tregnaghi 2011-LA	6	4211	17	2099	16.9%	0.18 [0.07 , 0.45]
Subtotal (95% CI)		**17842**		**13802**	**100.0%**	**0.24 [0.14 , 0.41]**
Total events:	74		254			

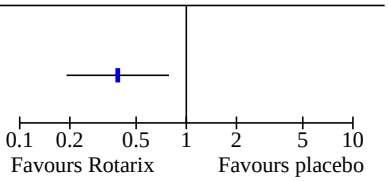
Heterogeneity: Tau² = 0.23; Chi² = 11.54, df = 4 (P = 0.02); I² = 65%

Test for overall effect: Z = 5.18 (P < 0.00001)



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

	Rotarix		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
1.34.1 Up to 1 year of follow-up (at least 1 rotavirus season)						
RIX Salinas 2005-LA	14	211	13	76	0.39 [0.19 , 0.79]	



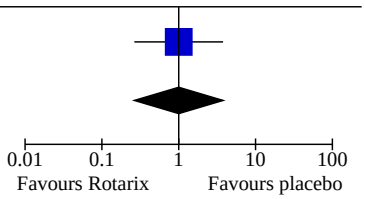
Analysis 1.35. Comparison 1: Rotarix versus placebo, Outcome 35: Subgroup analysis: rotavirus diarrhoea in HIV-infected children

	Rotarix		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
RIX Steele 2010a-ZAF	4	50	4	50	100.0%	1.00 [0.26 , 3.78]	
Total (95% CI)		**50**		**50**	**100.0%**	**1.00 [0.26 , 3.78]**	
Total events:	4		4				

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)

Test for subgroup differences: Not applicable



Comparison 2. RotaTeq versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Rotavirus diarrhoea: severe (up to 1 year follow-up)	10	14463	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.09, 0.42]
2.1.1 Low-mortality countries	5	7688	Risk Ratio (M-H, Random, 95% CI)	0.03 [0.01, 0.11]
2.1.2 High-mortality countries	5	6775	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.29, 0.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Rotavirus diarrhoea: severe (in 2nd year)	7	8677	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.32, 0.92]
2.2.1 Low-mortality countries	2	2596	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.02, 0.33]
2.2.2 High-mortality countries	5	6081	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.55, 0.99]
2.3 Rotavirus diarrhoea: severe (up to 2 years follow-up)	8	16049	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.17, 0.55]
2.3.1 Low-mortality countries	2	5442	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.01, 0.11]
2.3.2 Medium-mortality countries	1	3863	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.11, 0.41]
2.3.3 High-mortality countries	5	6744	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.41, 0.77]
2.4 All-cause diarrhoea: severe cases (up to 1 year follow-up)	3	4085	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.11]
2.4.1 High-mortality countries	3	4085	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.11]
2.5 All-cause diarrhoea: severe cases (up to 2 years follow-up)	4	5977	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.74, 0.99]
2.5.1 High-mortality countries	4	5977	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.74, 0.99]
2.6 All-cause death	14	84448	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.74, 1.26]
2.6.1 Low-mortality countries	6	72654	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.69, 2.22]
2.6.2 Medium-mortality countries	2	4088	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.18]
2.6.3 High-mortality countries	6	7706	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.68, 1.23]
2.7 All serious adverse events	14	82502	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.01]
2.7.1 Low-mortality countries	5	70690	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.84, 1.01]
2.7.2 Medium-mortality countries	2	4082	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.14, 3.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7.3 High-mortality countries	7	7730	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.72, 1.36]
2.8 Serious adverse events: intussusception	16	85495	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.38, 1.42]
2.8.1 Low-mortality countries	9	73925	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.35, 1.38]
2.8.2 Medium-mortality countries	2	4082	Risk Ratio (M-H, Random, 95% CI)	5.01 [0.24, 104.29]
2.8.3 High-mortality countries	5	7488	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.16]
2.9 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)	8	13450	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.28, 0.50]
2.9.1 Low-mortality countries	5	8644	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.25, 0.37]
2.9.2 High-mortality countries	3	4806	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.94]
2.10 Rotavirus diarrhoea: of any severity (2nd year of life)	2	2396	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.22, 0.90]
2.10.1 Low-mortality countries	1	1569	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.26, 0.55]
2.10.2 High-mortality countries	1	827	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.20, 4.91]
2.11 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)	7	15831	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.30, 0.65]
2.11.1 Low-mortality countries	2	5223	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.25, 0.37]
2.11.2 Medium-mortality countries	1	3864	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.21, 0.46]
2.11.3 High-mortality countries	4	6744	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.45, 0.83]
2.12 All-cause diarrhoea: of any severity (up to 1 year follow-up)	1	1059	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.61, 1.11]
2.12.1 High-mortality countries	1	1059	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.61, 1.11]
2.13 All-cause diarrhoea: of any severity (up to 2 years follow-up)	1	1059	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.68, 1.16]

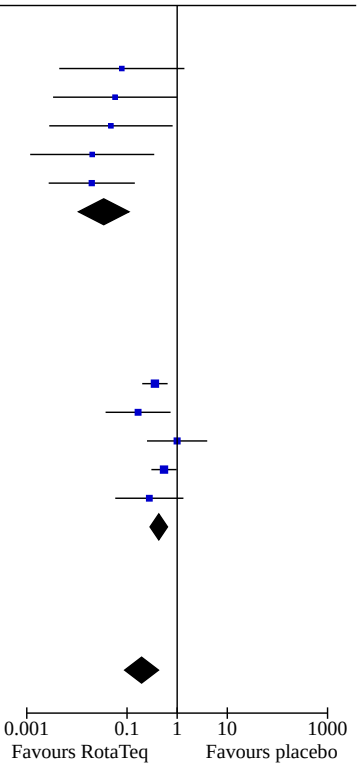
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.13.1 High-mortality countries	1	1059	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.68, 1.16]
2.14 All-cause hospitalizations (up to 2 years follow-up)	1	202	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.42, 3.49]
2.14.1 High-mortality countries	1	202	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.42, 3.49]
2.15 Rotavirus diarrhoea: requiring hospitalization	1	57134	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.02, 0.10]
2.15.1 Up to 1 year of follow-up	1	57134	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.02, 0.10]
2.16 Rotavirus diarrhoea: requiring medical attention	1	57134	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.04, 0.12]
2.16.1 Up to 1 year of follow-up	1	57134	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.04, 0.12]
2.17 Reactogenicity: fever	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.17.1 After dose 1	4	7124	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.91, 1.45]
2.17.2 After dose 2	2	4322	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.69, 1.01]
2.17.3 After dose 3	2	4294	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.90, 1.27]
2.17.4 End of follow-up	11	18391	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.09]
2.18 Reactogenicity: diarrhoea	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.18.1 After dose 1	2	4745	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.95, 1.31]
2.18.2 After dose 2	1	3905	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.72, 1.10]
2.18.3 End of follow-up	10	17087	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.11]
2.19 Reactogenicity: vomiting	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.19.1 After dose 1	2	4745	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.19.2 After dose 2	1	3905	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.32, 1.49]
2.19.3 After dose 3	1	3878	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.16, 1.32]
2.19.4 End of follow-up	9	16294	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.07]
2.20 Adverse events requiring discontinuation (end of follow-up)	10	15471	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.46, 1.56]
2.21 Dropouts before the end of the trial	13	85855	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.08]
2.22 Subgroup analysis: rotavirus diarrhoea of any severity (by G- or P-type)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.22.1 G1	4	11022	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.21, 0.32]
2.22.2 G2	3	9907	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.16, 0.78]
2.22.3 G3	4	11022	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.08, 2.02]
2.22.4 G4	3	9907	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.13, 1.33]
2.22.5 G9	2	9537	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.20, 0.54]
2.22.6 P8	1	3864	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.21, 0.46]
2.23 Subgroup analysis: severe cases of rotavirus diarrhoea (by G- or P-type)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.23.1 G1	3	75909	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.03, 1.73]
2.23.2 G2	3	75909	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.13, 1.35]
2.23.3 G3	3	75909	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.05, 2.72]
2.23.4 G4	3	75909	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.03, 0.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.23.5 G8	1	4008	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.02, 0.99]
2.23.6 G9	3	75909	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.05, 0.33]
2.23.7 P4	1	4008	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.39, 1.66]
2.23.8 P6	1	4008	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.86]
2.23.9 P8	2	7872	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.13, 1.12]
2.24 Subgroup analysis: HIV-infected children	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.24.1 Rotavirus diarrhoea: severe (up to two years follow-up)	1	38	Risk Ratio (M-H, Random, 95% CI)	2.45 [0.11, 56.68]
2.24.2 All-cause diarrhoea: severe (up to two years follow-up)	1	38	Risk Ratio (M-H, Random, 95% CI)	4.05 [0.52, 31.43]
2.24.3 All-cause death	2	114	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.53, 3.45]
2.24.4 Serious adverse events (up to 24 weeks)	2	113	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.59, 3.97]

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

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Low-mortality countries						
TEQ Block 2007-EU/USA	0	551	6	564	5.3%	0.08 [0.00 , 1.39]
TEQ Clark 2004-USA	0	187	8	183	5.4%	0.06 [0.00 , 0.99]
TEQ Iwata 2013-JPN	0	380	10	381	5.4%	0.05 [0.00 , 0.81]
TEQ Vesikari 2006a-FIN	0	765	8	262	5.4%	0.02 [0.00 , 0.35]
TEQ Vesikari 2006b-INT (1)	1	2198	51	2217	8.6%	0.02 [0.00 , 0.14]
Subtotal (95% CI)		**4081**		**3607**	**30.1%**	**0.03 [0.01 , 0.11]**
Total events:	1		83			
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 4 (P = 0.92); I² = 0%						
Test for overall effect: Z = 5.72 (P < 0.00001)						
2.1.2 High-mortality countries						
TEQ Armah 2010-GHA (2)	15	981	42	989	17.7%	0.36 [0.20 , 0.64]
TEQ Armah 2010-KEN (3)	2	575	12	573	11.4%	0.17 [0.04 , 0.74]
TEQ Armah 2010-MLI (4)	4	845	4	843	12.1%	1.00 [0.25 , 3.98]
TEQ Zaman 2010-BGD (5)	17	556	31	554	17.7%	0.55 [0.31 , 0.98]
TEQ Zaman 2010-VNM (6)	2	435	7	424	10.9%	0.28 [0.06 , 1.33]
Subtotal (95% CI)		**3392**		**3383**	**69.9%**	**0.43 [0.29 , 0.64]**
Total events:	40		96			
Heterogeneity: Tau² = 0.02; Chi² = 4.33, df = 4 (P = 0.36); I² = 8%						
Test for overall effect: Z = 4.14 (P < 0.0001)						
Total (95% CI)		**7473**		**6990**	**100.0%**	**0.20 [0.09 , 0.42]**
Total events:	41		179			
Heterogeneity: Tau² = 0.79; Chi² = 26.61, df = 9 (P = 0.002); I² = 66%						
Test for overall effect: Z = 4.13 (P < 0.0001)						
Test for subgroup differences: Chi² = 16.41, df = 1 (P < 0.0001), I² = 93.9%						

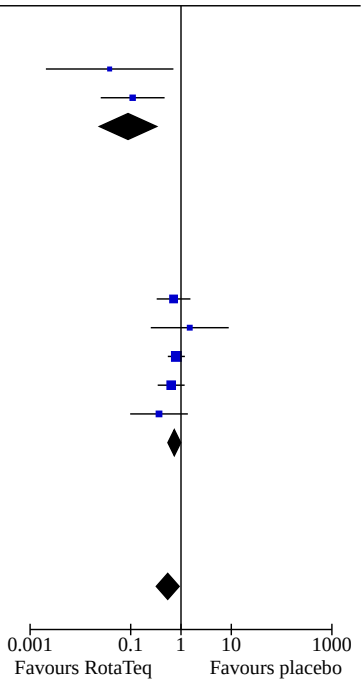


Footnotes

(1) Multinational study: mainly low-mortality countries (n=8) but also three medium- and one high-mortality country
(2) Total number of participants taken from Tapia et al. 2012, Table 4, data for Ghana only.
(3) Total number of participants taken from Tapia et al. 2012, Table 4, data for Kenya only.
(4) Total number of participants taken from Tapia et al. 2012, Table 4, data for Mali only.
(5) Data from RV5 Zaman 2010-AS for Bangladesh only
(6) Data from RV5 Zaman 2010-AS for Vietnam only

Analysis 2.2. Comparison 2: RotaTeq versus placebo, Outcome 2: Rotavirus diarrhoea: severe (in 2nd year)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Low-mortality countries						
TEQ Vesikari 2006a-FIN	0	765	4	262	2.9%	0.04 [0.00 , 0.71]
TEQ Vesikari 2006b-INT (1)	2	813	17	756	9.2%	0.11 [0.03 , 0.47]
Subtotal (95% CI)		**1578**		**1018**	**12.1%**	**0.09 [0.02 , 0.33]**
Total events:	2		21			
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 3.64 (P = 0.0003)						
2.2.2 High-mortality countries						
TEQ Armah 2010-GHA	11	828	15	803	19.3%	0.71 [0.33 , 1.54]
TEQ Armah 2010-KEN	3	414	2	412	6.8%	1.49 [0.25 , 8.89]
TEQ Armah 2010-MLI	43	829	53	826	28.2%	0.81 [0.55 , 1.19]
TEQ Zaman 2010-BGD	16	556	25	554	22.8%	0.64 [0.34 , 1.18]
TEQ Zaman 2010-VNM	3	435	8	424	10.6%	0.37 [0.10 , 1.37]
Subtotal (95% CI)		**3062**		**3019**	**87.9%**	**0.74 [0.55 , 0.99]**
Total events:	76		103			
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 4 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Total (95% CI)		**4640**		**4037**	**100.0%**	**0.54 [0.32 , 0.92]**
Total events:	78		124			
Heterogeneity: Tau² = 0.21; Chi² = 12.50, df = 6 (P = 0.05); I² = 52%						
Test for overall effect: Z = 2.28 (P = 0.02)						
Test for subgroup differences: Chi² = 9.61, df = 1 (P = 0.002), I² = 89.6%						

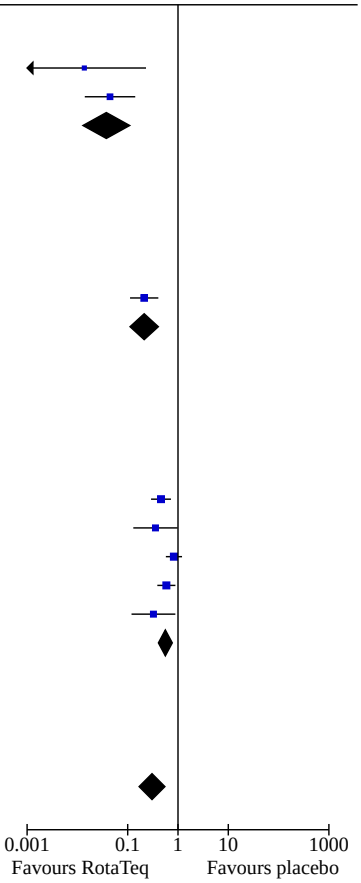


Footnotes

(1) Multinational study: mainly low-mortality countries (n=8) but also three medium- and one high-mortality country

Analysis 2.3. Comparison 2: RotaTeq versus placebo, Outcome 3: Rotavirus diarrhoea: severe (up to 2 years follow-up)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Low-mortality countries						
TEQ Vesikari 2006a-FIN	0	765	12	262	3.5%	0.01 [0.00 , 0.23]
TEQ Vesikari 2006b-INT (1)	3	2198	68	2217	10.5%	0.04 [0.01 , 0.14]
Subtotal (95% CI)		**2963**		**2479**	**14.0%**	**0.04 [0.01 , 0.11]**
Total events:	3		80			
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 6.02 (P < 0.00001)						
2.3.2 Medium-mortality countries						
TEQ Mo 2017-CHN	11	1926	52	1937	14.5%	0.21 [0.11 , 0.41]
Subtotal (95% CI)		**1926**		**1937**	**14.5%**	**0.21 [0.11 , 0.41]**
Total events:	11		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.69 (P < 0.00001)						
2.3.3 High-mortality countries						
TEQ Armah 2010-GHA (2)	26	982	57	989	15.9%	0.46 [0.29 , 0.72]
TEQ Armah 2010-KEN (3)	5	569	14	568	11.5%	0.36 [0.13 , 0.98]
TEQ Armah 2010-MLI (4)	48	832	58	835	16.4%	0.83 [0.57 , 1.20]
TEQ Zaman 2010-BGD	33	556	56	554	16.1%	0.59 [0.39 , 0.89]
TEQ Zaman 2010-VNM	5	435	15	424	11.6%	0.32 [0.12 , 0.89]
Subtotal (95% CI)		**3374**		**3370**	**71.5%**	**0.56 [0.41 , 0.77]**
Total events:	117		200			
Heterogeneity: Tau² = 0.05; Chi² = 6.76, df = 4 (P = 0.15); I² = 41%						
Test for overall effect: Z = 3.58 (P = 0.0003)						
Total (95% CI)		**8263**		**7786**	**100.0%**	**0.30 [0.17 , 0.55]**
Total events:	131		332			
Heterogeneity: Tau² = 0.52; Chi² = 42.92, df = 7 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 3.95 (P < 0.0001)						
Test for subgroup differences: Chi² = 26.77, df = 2 (P < 0.00001), I² = 92.5%						



Footnotes

(1) Multinational study: mainly low-mortality countries (n=8) but also three medium- and one high-mortality country

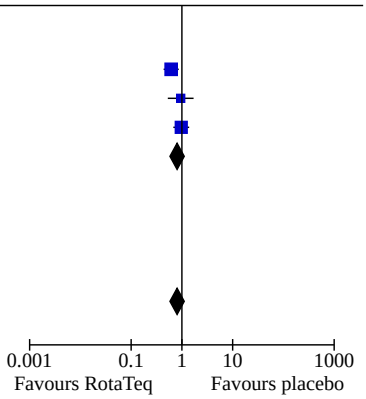
(2) Total number of participants taken from Tapia et al. 2012, Table 4, data for Ghana only.

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

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

Analysis 2.4. Comparison 2: RotaTeq versus placebo, Outcome 4: All-cause diarrhoea: severe cases (up to 1 year follow-up)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 High-mortality countries						
TEQ Armah 2010-GHA (1)	49	753	78	737	40.1%	0.61 [0.44 , 0.87]
TEQ Armah 2010-KEN (2)	21	481	22	477	21.6%	0.95 [0.53 , 1.70]
TEQ Armah 2010-MLI (3)	55	823	56	814	38.4%	0.97 [0.68 , 1.39]
Subtotal (95% CI)		**2057**		**2028**	**100.0%**	**0.80 [0.58 , 1.11]**
Total events:	125		156			
Heterogeneity: Tau² = 0.04; Chi² = 3.70, df = 2 (P = 0.16); I² = 46%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Total (95% CI)		**2057**		**2028**	**100.0%**	**0.80 [0.58 , 1.11]**
Total events:	125		156			
Heterogeneity: Tau² = 0.04; Chi² = 3.70, df = 2 (P = 0.16); I² = 46%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Test for subgroup differences: Not applicable						

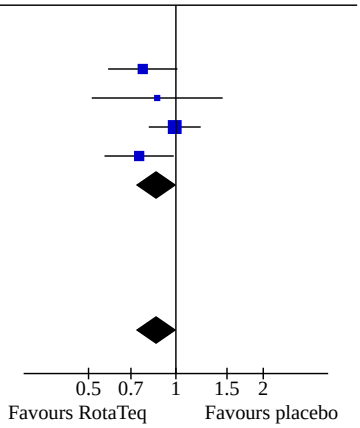


Footnotes

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

Analysis 2.5. Comparison 2: RotaTeq versus placebo, Outcome 5: All-cause diarrhoea: severe cases (up to 2 years follow-up)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 High-mortality countries						
TEQ Armah 2010-GHA (1)	80	747	101	725	25.5%	0.77 [0.58 , 1.01]
TEQ Armah 2010-KEN (2)	25	472	29	472	8.0%	0.86 [0.51 , 1.45]
TEQ Armah 2010-MLI (3)	147	797	148	795	40.9%	0.99 [0.81 , 1.22]
TEQ Zaman 2010-AS (4)	81	991	107	978	25.6%	0.75 [0.57 , 0.98]
Subtotal (95% CI)		**3007**		**2970**	**100.0%**	**0.85 [0.74 , 0.99]**
Total events:	333		385			
Heterogeneity: Tau² = 0.00; Chi² = 3.47, df = 3 (P = 0.32); I² = 14%						
Test for overall effect: Z = 2.05 (P = 0.04)						
Total (95% CI)		**3007**		**2970**	**100.0%**	**0.85 [0.74 , 0.99]**
Total events:	333		385			
Heterogeneity: Tau² = 0.00; Chi² = 3.47, df = 3 (P = 0.32); I² = 14%						
Test for overall effect: Z = 2.05 (P = 0.04)						
Test for subgroup differences: Not applicable						

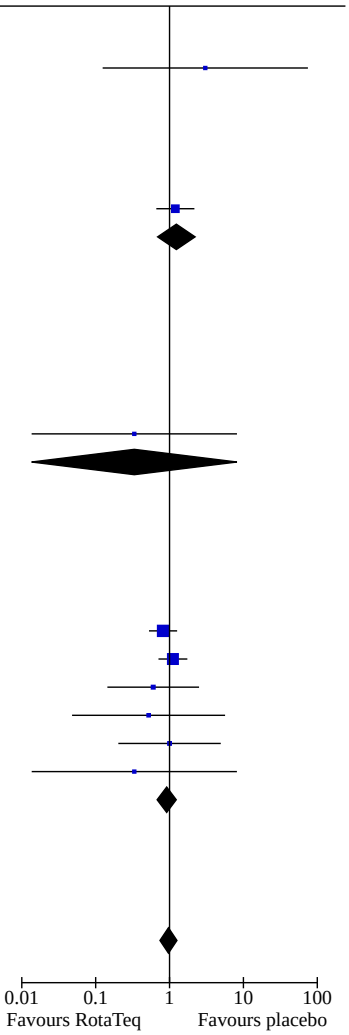


Footnotes

(1) Data collected from Tapia et al. 2012, Table 3, data for Ghana only.
(2) Data collected from Tapia et al. 2012, Table 3, data for Kenya only.
(3) Data collected from Tapia et al. 2012, Table 3, data for Mali only.
(4) This study was mainly conducted in high mortality Bangladesh, but also in low mortality Vietnam.

Analysis 2.6. Comparison 2: RotaTeq versus placebo, Outcome 6: All-cause death

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Low-mortality countries						
TEQ Block 2007-EU/USA	1	650	0	660	0.7%	3.05 [0.12 , 74.64]
TEQ Ciarlet 2009-EU	0	201	0	202		Not estimable
TEQ Iwata 2013-JPN	0	380	0	381		Not estimable
TEQ Merck[009] 2005-USA	0	680	0	113		Not estimable
TEQ Vesikari 2006a-FIN	0	1027	0	322		Not estimable
TEQ Vesikari 2006b-INT (1)	24	34035	20	34003	19.8%	1.20 [0.66 , 2.17]
Subtotal (95% CI)		**36973**		**35681**	**20.5%**	**1.24 [0.69 , 2.22]**
Total events:	25		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
2.6.2 Medium-mortality countries						
TEQ Lawrence 2012-CHN	0	24	0	24		Not estimable
TEQ Mo 2017-CHN	0	2020	1	2020	0.7%	0.33 [0.01 , 8.18]
Subtotal (95% CI)		**2044**		**2044**	**0.7%**	**0.33 [0.01 , 8.18]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
2.6.3 High-mortality countries						
TEQ Armah 2010-GHA	35	1098	43	1102	36.3%	0.82 [0.53 , 1.27]
TEQ Armah 2010-KEN	38	656	34	652	34.5%	1.11 [0.71 , 1.74]
TEQ Armah 2010-MLI	3	979	5	981	3.4%	0.60 [0.14 , 2.51]
TEQ Levin 2017-AF (2)	1	99	2	103	1.2%	0.52 [0.05 , 5.65]
TEQ Zaman 2010-BGD	3	568	3	568	2.7%	1.00 [0.20 , 4.93]
TEQ Zaman 2010-VNM	0	450	1	450	0.7%	0.33 [0.01 , 8.16]
Subtotal (95% CI)		**3850**		**3856**	**78.8%**	**0.91 [0.68 , 1.23]**
Total events:	80		88			
Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 5 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.59 (P = 0.56)						
Total (95% CI)		**42867**		**41581**	**100.0%**	**0.97 [0.74 , 1.26]**
Total events:	105		109			
Heterogeneity: Tau² = 0.00; Chi² = 3.47, df = 8 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.80)						
Test for subgroup differences: Chi² = 1.24, df = 2 (P = 0.54), I² = 0%						



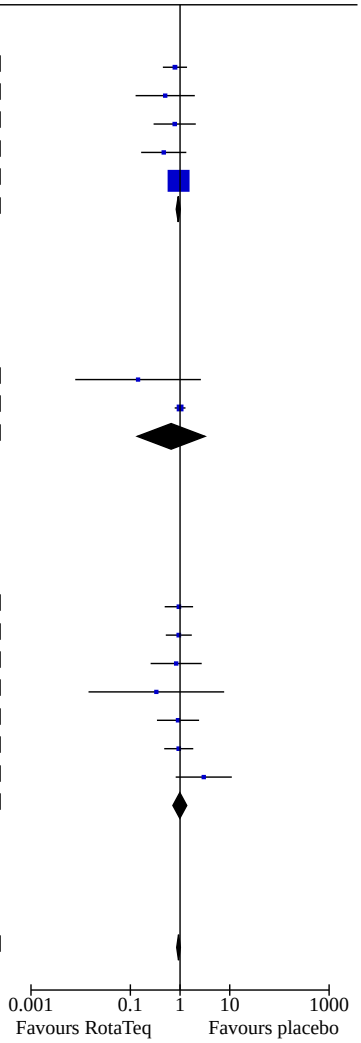
Footnotes

(1) Multinational study: mainly low-mortality countries (n=8) but also three medium- and one high-mortality country

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

Analysis 2.7. Comparison 2: RotaTeq versus placebo, Outcome 7: All serious adverse events

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 Low-mortality countries						
TEQ Block 2007-EU/USA	21	650	27	660	2.2%	0.79 [0.45 , 1.38]
TEQ Ciarlet 2009-EU	3	201	6	202	0.4%	0.50 [0.13 , 1.98]
TEQ Iwata 2013-JPN	7	380	9	381	0.7%	0.78 [0.29 , 2.07]
TEQ Kim 2008-KOR	6	115	7	63	0.6%	0.47 [0.16 , 1.34]
TEQ Vesikari 2006b-INT (1)	803	34035	859	34003	77.8%	0.93 [0.85 , 1.03]
Subtotal (95% CI)		**35381**		**35309**	**81.8%**	**0.92 [0.84 , 1.01]**
Total events:	840		908			
Heterogeneity: Tau² = 0.00; Chi² = 2.83, df = 4 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.75 (P = 0.08)						
2.7.2 Medium-mortality countries						
TEQ Lawrence 2012-CHN	0	24	3	24	0.1%	0.14 [0.01 , 2.62]
TEQ Mo 2017-CHN	116	2015	116	2019	11.3%	1.00 [0.78 , 1.29]
Subtotal (95% CI)		**2039**		**2043**	**11.3%**	**0.66 [0.14 , 3.17]**
Total events:	116		119			
Heterogeneity: Tau² = 0.79; Chi² = 1.72, df = 1 (P = 0.19); I² = 42%						
Test for overall effect: Z = 0.52 (P = 0.61)						
2.7.3 High-mortality countries						
TEQ Armah 2010-GHA	17	1098	18	1102	1.6%	0.95 [0.49 , 1.83]
TEQ Armah 2010-KEN	20	649	21	643	1.9%	0.94 [0.52 , 1.72]
TEQ Armah 2010-MLI	5	979	6	981	0.5%	0.84 [0.26 , 2.73]
TEQ Dhingra 2014-IND	0	20	1	20	0.1%	0.33 [0.01 , 7.72]
TEQ Levin 2017-AF (2)	7	99	8	103	0.7%	0.91 [0.34 , 2.42]
TEQ Zaman 2010-BGD	16	568	17	568	1.6%	0.94 [0.48 , 1.84]
TEQ Zaman 2010-VNM	9	450	3	450	0.4%	3.00 [0.82 , 11.01]
Subtotal (95% CI)		**3863**		**3867**	**6.8%**	**0.99 [0.72 , 1.36]**
Total events:	74		74			
Heterogeneity: Tau² = 0.00; Chi² = 3.43, df = 6 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						
Total (95% CI)		**41283**		**41219**	**100.0%**	**0.93 [0.86 , 1.01]**
Total events:	1030		1101			
Heterogeneity: Tau² = 0.00; Chi² = 8.37, df = 13 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Chi² = 0.35, df = 2 (P = 0.84), I² = 0%						



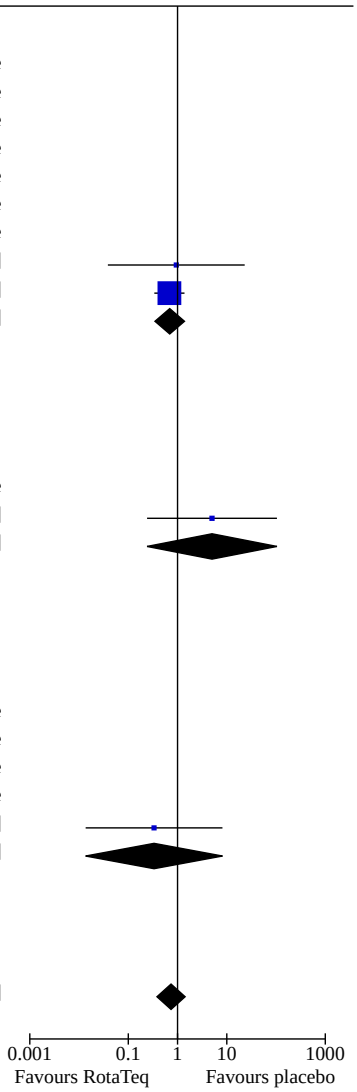
Footnotes

(1) Multinational study: mainly low-mortality countries (n=8) but also three medium- and one high-mortality country

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

Analysis 2.8. Comparison 2: RotaTeq versus placebo, Outcome 8: Serious adverse events: intussusception

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Low-mortality countries						
TEQ Block 2007-EU/USA	0	650	0	660		Not estimable
TEQ Ciarlet 2009-EU	0	201	0	202		Not estimable
TEQ Clark 2003-USA	0	573	0	148		Not estimable
TEQ Clark 2004-USA	0	218	0	221		Not estimable
TEQ Iwata 2013-JPN	0	380	0	381		Not estimable
TEQ Kim 2008-KOR	0	115	0	63		Not estimable
TEQ Merck[009] 2005-USA	0	680	0	113		Not estimable
TEQ Vesikari 2006a-FIN	1	1027	0	322	4.2%	0.94 [0.04 , 23.08]
TEQ Vesikari 2006b-INT (1)	13	34002	19	33969	86.9%	0.68 [0.34 , 1.38]
Subtotal (95% CI)		**37846**		**36079**	**91.1%**	**0.69 [0.35 , 1.38]**
Total events:	14		19			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.04 (P = 0.30)						
2.8.2 Medium-mortality countries						
TEQ Lawrence 2012-CHN	0	24	0	24		Not estimable
TEQ Mo 2017-CHN	2	2015	0	2019	4.7%	5.01 [0.24 , 104.29]
Subtotal (95% CI)		**2039**		**2043**	**4.7%**	**5.01 [0.24 , 104.29]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
2.8.3 High-mortality countries						
TEQ Armah 2010-GHA	0	1098	0	1102		Not estimable
TEQ Armah 2010-KEN	0	649	0	643		Not estimable
TEQ Armah 2010-MLI	0	979	0	981		Not estimable
TEQ Zaman 2010-BGD	0	568	0	568		Not estimable
TEQ Zaman 2010-VNM	0	450	1	450	4.2%	0.33 [0.01 , 8.16]
Subtotal (95% CI)		**3744**		**3744**	**4.2%**	**0.33 [0.01 , 8.16]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**43629**		**41866**	**100.0%**	**0.74 [0.38 , 1.42]**
Total events:	16		20			
Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
Test for subgroup differences: Chi² = 1.80, df = 2 (P = 0.41), I² = 0%						

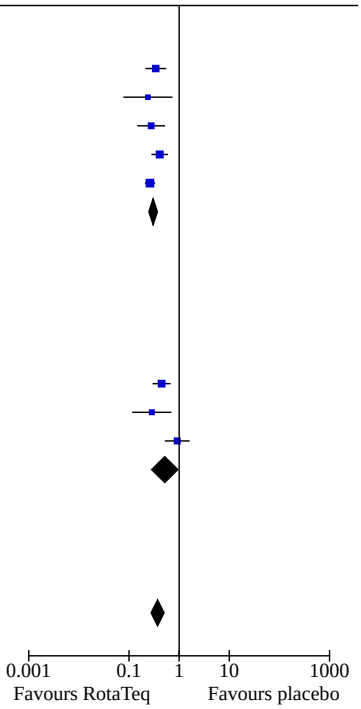


Footnotes

(1) Multinational study: mainly low-mortality countries (n=8) but also three medium- and one high-mortality country

Analysis 2.9. Comparison 2: RotaTeq versus placebo, Outcome 9: Rotavirus diarrhoea: of any severity (up to 1 year follow-up)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 Low-mortality countries						
TEQ Block 2007-EU/USA	21	551	63	564	13.9%	0.34 [0.21 , 0.55]
TEQ Clark 2003-USA	5	342	7	114	5.2%	0.24 [0.08 , 0.74]
TEQ Clark 2004-USA	11	187	39	183	10.9%	0.28 [0.15 , 0.52]
TEQ Vesikari 2006a-FIN	51	766	43	264	16.1%	0.41 [0.28 , 0.60]
TEQ Vesikari 2006b-INT (1)	83	2834	318	2839	19.2%	0.26 [0.21 , 0.33]
Subtotal (95% CI)		**4680**		**3964**	**65.3%**	**0.30 [0.25 , 0.37]**
Total events:	171		470			
Heterogeneity: Tau² = 0.01; Chi² = 4.41, df = 4 (P = 0.35); I² = 9%						
Test for overall effect: Z = 12.02 (P < 0.00001)						
2.9.2 High-mortality countries						
TEQ Armah 2010-GHA	31	981	70	989	15.3%	0.45 [0.30 , 0.68]
TEQ Armah 2010-KEN	6	575	21	573	7.2%	0.28 [0.12 , 0.70]
TEQ Armah 2010-MLI	22	845	24	843	12.1%	0.91 [0.52 , 1.62]
Subtotal (95% CI)		**2401**		**2405**	**34.7%**	**0.52 [0.28 , 0.94]**
Total events:	59		115			
Heterogeneity: Tau² = 0.18; Chi² = 6.02, df = 2 (P = 0.05); I² = 67%						
Test for overall effect: Z = 2.16 (P = 0.03)						
Total (95% CI)		**7081**		**6369**	**100.0%**	**0.37 [0.28 , 0.50]**
Total events:	230		585			
Heterogeneity: Tau² = 0.10; Chi² = 19.91, df = 7 (P = 0.006); I² = 65%						
Test for overall effect: Z = 6.57 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.75, df = 1 (P = 0.10), I² = 63.6%						

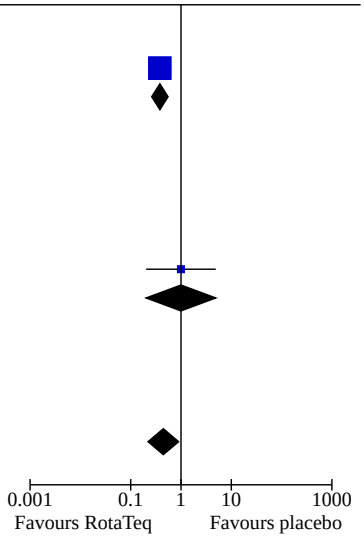


Footnotes

(1) Multinational study: mainly low-mortality countries (n=8) but also three medium- and one high-mortality country

Analysis 2.10. Comparison 2: RotaTeq versus placebo, Outcome 10: Rotavirus diarrhoea: of any severity (2nd year of life)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 Low-mortality countries						
TEQ Vesikari 2006b-INT (1)	36	813	88	756	83.6%	0.38 [0.26 , 0.55]
Subtotal (95% CI)		**813**		**756**	**83.6%**	**0.38 [0.26 , 0.55]**
Total events:	36		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.05 (P < 0.00001)						
2.10.2 High-mortality countries						
TEQ Armah 2010-KEN	3	414	3	413	16.4%	1.00 [0.20 , 4.91]
Subtotal (95% CI)		**414**		**413**	**16.4%**	**1.00 [0.20 , 4.91]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**1227**		**1169**	**100.0%**	**0.45 [0.22 , 0.90]**
Total events:	39		91			
Heterogeneity: Tau² = 0.12; Chi² = 1.33, df = 1 (P = 0.25); I² = 25%						
Test for overall effect: Z = 2.27 (P = 0.02)						
Test for subgroup differences: Chi² = 1.33, df = 1 (P = 0.25), I² = 24.9%						

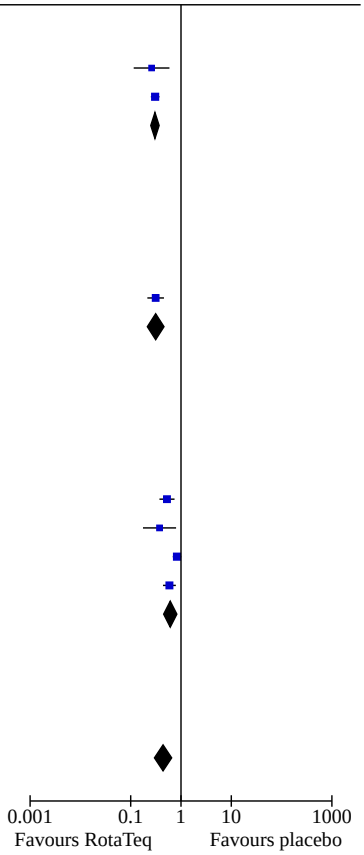


Footnotes

(1) only G1–G4 cases, multinational study: mainly low-mortality countries (n=8) but also three medium- and one high-mortality country

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

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.11.1 Low-mortality countries						
TEQ Iwata 2013-JPN	7	355	27	356	9.9%	0.26 [0.11 , 0.59]
TEQ Vesikari 2006b-INT (1)	119	2207	406	2305	16.7%	0.31 [0.25 , 0.37]
Subtotal (95% CI)		**2562**		**2661**	**26.6%**	**0.30 [0.25 , 0.37]**
Total events:	126		433			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 12.28 (P < 0.00001)						
2.11.2 Medium-mortality countries						
TEQ Mo 2017-CHN	34	1927	109	1937	15.0%	0.31 [0.21 , 0.46]
Subtotal (95% CI)		**1927**		**1937**	**15.0%**	**0.31 [0.21 , 0.46]**
Total events:	34		109			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.99 (P < 0.00001)						
2.11.3 High-mortality countries						
TEQ Armah 2010-GHA	46	982	88	989	15.3%	0.53 [0.37 , 0.74]
TEQ Armah 2010-KEN	9	569	24	568	10.6%	0.37 [0.18 , 0.80]
TEQ Armah 2010-MLI	151	832	182	835	16.7%	0.83 [0.69 , 1.01]
TEQ Zaman 2010-AS	65	991	109	978	15.9%	0.59 [0.44 , 0.79]
Subtotal (95% CI)		**3374**		**3370**	**58.4%**	**0.61 [0.45 , 0.83]**
Total events:	271		403			
Heterogeneity: Tau² = 0.06; Chi² = 9.72, df = 3 (P = 0.02); I² = 69%						
Test for overall effect: Z = 3.21 (P = 0.001)						
Total (95% CI)		**7863**		**7968**	**100.0%**	**0.44 [0.30 , 0.65]**
Total events:	431		945			
Heterogeneity: Tau² = 0.23; Chi² = 61.92, df = 6 (P < 0.00001); I² = 90%						
Test for overall effect: Z = 4.10 (P < 0.0001)						
Test for subgroup differences: Chi² = 15.51, df = 2 (P = 0.0004), I² = 87.1%						

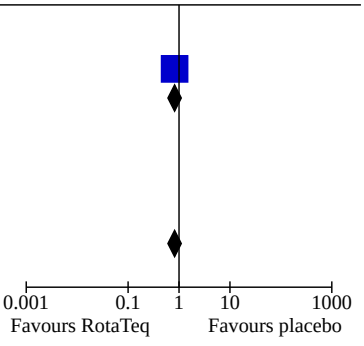


Footnotes

(1) 2nd season only G1-G4, multinational study: mainly low-mortality countries (n=8) but also three medium- and one high-mortality country

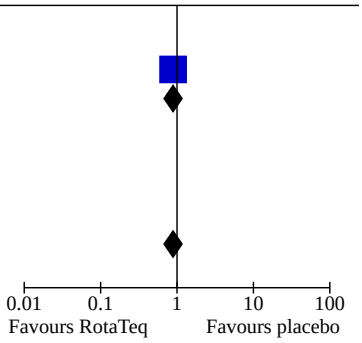
Analysis 2.12. Comparison 2: RotaTeq versus placebo, Outcome 12: All-cause diarrhoea: of any severity (up to 1 year follow-up)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 High-mortality countries						
TEQ Armah 2010-KEN	66	525	82	534	100.0%	0.82 [0.61 , 1.11]
Subtotal (95% CI)		**525**		**534**	**100.0%**	**0.82 [0.61 , 1.11]**
Total events:	66		82			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Total (95% CI)		**525**		**534**	**100.0%**	**0.82 [0.61 , 1.11]**
Total events:	66		82			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: Not applicable						



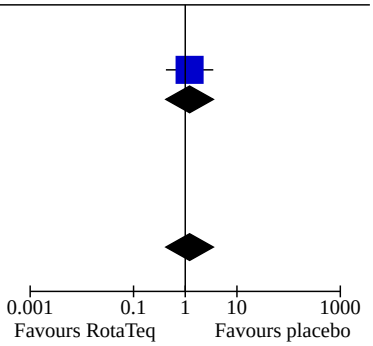
Analysis 2.13. Comparison 2: RotaTeq versus placebo, Outcome 13: All-cause diarrhoea: of any severity (up to 2 years follow-up)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.13.1 High-mortality countries						
TEQ Armah 2010-KEN	82	525	94	534	100.0%	0.89 [0.68 , 1.16]
Subtotal (95% CI)		**525**		**534**	**100.0%**	**0.89 [0.68 , 1.16]**
Total events:	82		94			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.39)						
Total (95% CI)		**525**		**534**	**100.0%**	**0.89 [0.68 , 1.16]**
Total events:	82		94			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.39)						
Test for subgroup differences: Not applicable						



Analysis 2.14. Comparison 2: RotaTeq versus placebo, Outcome 14: All-cause hospitalizations (up to 2 years follow-up)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.14.1 High-mortality countries						
TEQ Levin 2017-AF (1)	7	99	6	103	100.0%	1.21 [0.42 , 3.49]
Subtotal (95% CI)		**99**		**103**	**100.0%**	**1.21 [0.42 , 3.49]**
Total events:	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)		**99**		**103**	**100.0%**	**1.21 [0.42 , 3.49]**
Total events:	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: Not applicable						

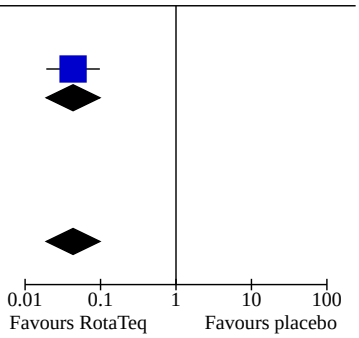


Footnotes

(1) HIV-exposed but uninfected and HIV-infected infants

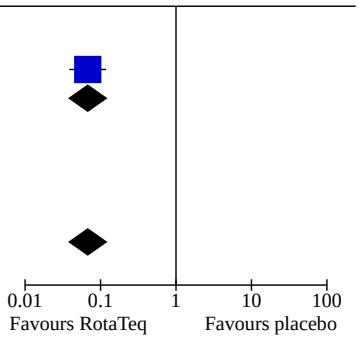
Analysis 2.15. Comparison 2: RotaTeq versus placebo, Outcome 15: Rotavirus diarrhoea: requiring hospitalization

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.15.1 Up to 1 year of follow-up						
TEQ Vesikari 2006b-INT	6	28646	138	28488	100.0%	0.04 [0.02 , 0.10]
Subtotal (95% CI)		**28646**		**28488**	**100.0%**	**0.04 [0.02 , 0.10]**
Total events:	6		138			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.53 (P < 0.00001)						
Total (95% CI)		**28646**		**28488**	**100.0%**	**0.04 [0.02 , 0.10]**
Total events:	6		138			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.53 (P < 0.00001)						
Test for subgroup differences: Not applicable						



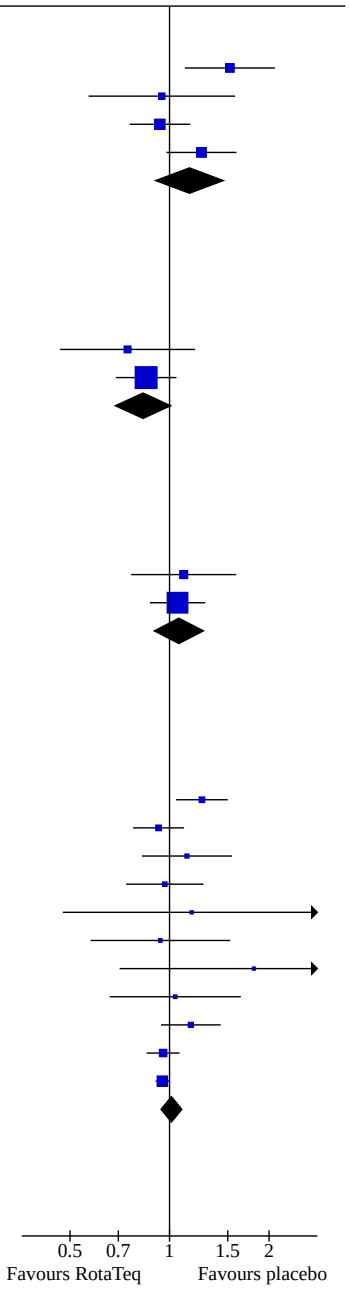
Analysis 2.16. Comparison 2: RotaTeq versus placebo, Outcome 16: Rotavirus diarrhoea: requiring medical attention

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.16.1 Up to 1 year of follow-up						
TEQ Vesikari 2006b-INT	13	28646	191	28488	100.0%	0.07 [0.04 , 0.12]
Subtotal (95% CI)		**28646**		**28488**	**100.0%**	**0.07 [0.04 , 0.12]**
Total events:	13		191			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.40 (P < 0.00001)						
Total (95% CI)		**28646**		**28488**	**100.0%**	**0.07 [0.04 , 0.12]**
Total events:	13		191			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.40 (P < 0.00001)						
Test for subgroup differences: Not applicable						



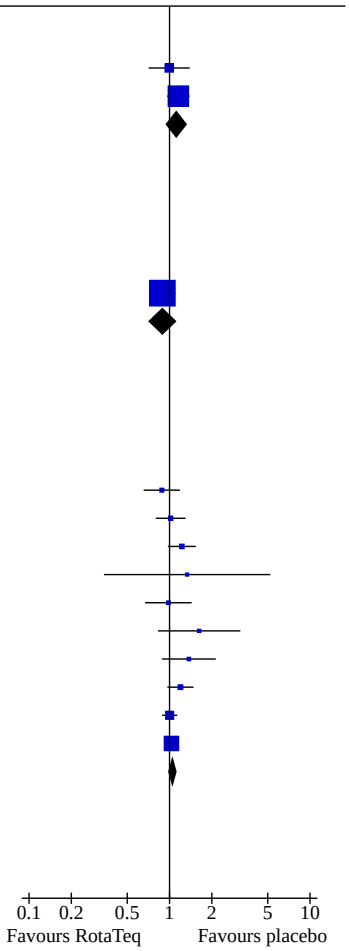
Analysis 2.17. Comparison 2: RotaTeq versus placebo, Outcome 17: Reactogenicity: fever

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.17.1 After dose 1						
TEQ Block 2007-EU/USA	87	650	58	660	24.4%	1.52 [1.11 , 2.09]
TEQ Clark 2004-USA	25	213	27	218	14.2%	0.95 [0.57 , 1.58]
TEQ Mo 2017-CHN	154	2015	165	2019	32.0%	0.94 [0.76 , 1.15]
TEQ Vesikari 2006a-FIN	255	1027	64	322	29.4%	1.25 [0.98 , 1.59]
Subtotal (95% CI)		**3905**		**3219**	**100.0%**	**1.15 [0.91 , 1.45]**
Total events:	521		314			
Heterogeneity: Tau² = 0.03; Chi² = 7.67, df = 3 (P = 0.05); I² = 61%						
Test for overall effect: Z = 1.16 (P = 0.25)						
2.17.2 After dose 2						
TEQ Clark 2004-USA	26	208	35	209	16.8%	0.75 [0.47 , 1.19]
TEQ Mo 2017-CHN	146	1946	173	1959	83.2%	0.85 [0.69 , 1.05]
Subtotal (95% CI)		**2154**		**2168**	**100.0%**	**0.83 [0.69 , 1.01]**
Total events:	172		208			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.88 (P = 0.06)						
2.17.3 After dose 3						
TEQ Clark 2004-USA	47	207	43	209	21.7%	1.10 [0.77 , 1.59]
TEQ Mo 2017-CHN	191	1932	182	1946	78.3%	1.06 [0.87 , 1.28]
Subtotal (95% CI)		**2139**		**2155**	**100.0%**	**1.07 [0.90 , 1.27]**
Total events:	238		225			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
2.17.4 End of follow-up						
TEQ Block 2007-EU/USA	195	650	158	660	11.3%	1.25 [1.05 , 1.50]
TEQ Ciarlet 2009-EU	106	201	115	202	11.5%	0.93 [0.78 , 1.11]
TEQ Clark 2003-USA	157	568	36	147	4.7%	1.13 [0.82 , 1.54]
TEQ Clark 2004-USA	70	218	73	220	6.0%	0.97 [0.74 , 1.27]
TEQ Dhingra 2014-IND	7	20	6	20	0.6%	1.17 [0.48 , 2.86]
TEQ Iwata 2013-JPN	29	380	31	381	2.1%	0.94 [0.58 , 1.52]
TEQ Lawrence 2012-CHN	9	24	5	24	0.6%	1.80 [0.71 , 4.59]
TEQ Levin 2017-AF	27	99	27	103	2.3%	1.04 [0.66 , 1.64]
TEQ Merck[009] 2005-USA	370	680	53	113	9.1%	1.16 [0.94 , 1.43]
TEQ Mo 2017-CHN	440	2015	461	2019	19.2%	0.96 [0.85 , 1.07]
TEQ Vesikari 2006b-INT	1974	4826	2073	4821	32.5%	0.95 [0.91 , 1.00]
Subtotal (95% CI)		**9681**		**8710**	**100.0%**	**1.01 [0.94 , 1.09]**
Total events:	3384		3038			
Heterogeneity: Tau² = 0.00; Chi² = 14.45, df = 10 (P = 0.15); I² = 31%						
Test for overall effect: Z = 0.36 (P = 0.72)						



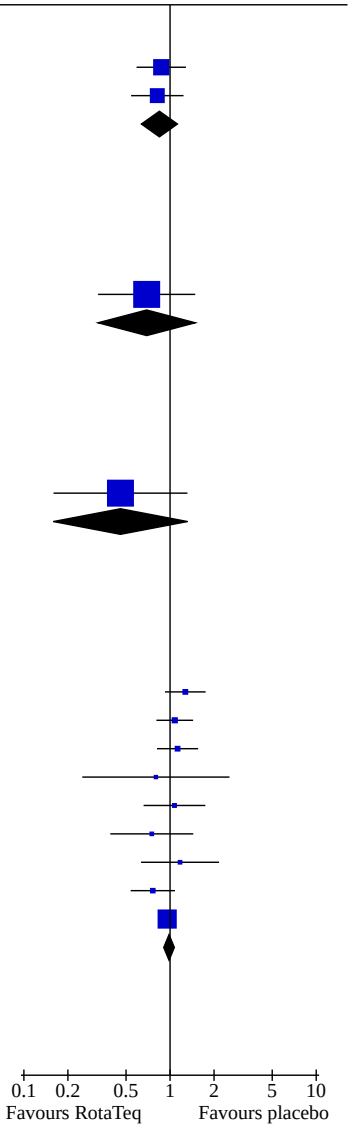
Analysis 2.18. Comparison 2: RotaTeq versus placebo, Outcome 18: Reactogenicity: diarrhoea

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.18.1 After dose 1						
TEQ Clark 2003-USA	127	565	33	146	23.1%	0.99 [0.71 , 1.39]
TEQ Mo 2017-CHN	218	2015	189	2019	76.9%	1.16 [0.96 , 1.39]
Subtotal (95% CI)		**2580**		**2165**	**100.0%**	**1.12 [0.95 , 1.31]**
Total events:	345		222			
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 1.33 (P = 0.18)						
2.18.2 After dose 2						
TEQ Mo 2017-CHN	143	1946	162	1959	100.0%	0.89 [0.72 , 1.10]
Subtotal (95% CI)		**1946**		**1959**	**100.0%**	**0.89 [0.72 , 1.10]**
Total events:	143		162			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
2.18.3 End of follow-up						
TEQ Ciarlet 2009-EU	57	201	65	202	3.8%	0.88 [0.65 , 1.19]
TEQ Clark 2003-USA	205	573	52	148	5.5%	1.02 [0.80 , 1.30]
TEQ Clark 2004-USA	97	218	80	220	6.3%	1.22 [0.97 , 1.54]
TEQ Dhingra 2014-IND	4	20	3	20	0.2%	1.33 [0.34 , 5.21]
TEQ Iwata 2013-JPN	46	380	47	381	2.3%	0.98 [0.67 , 1.44]
TEQ Lawrence 2012-CHN	13	24	8	24	0.7%	1.63 [0.83 , 3.19]
TEQ Levin 2017-AF	33	99	25	103	1.7%	1.37 [0.88 , 2.13]
TEQ Merck[009] 2005-USA	367	680	51	113	7.2%	1.20 [0.96 , 1.48]
TEQ Mo 2017-CHN	406	2015	406	2019	22.0%	1.00 [0.89 , 1.13]
TEQ Vesikari 2006b-INT	951	4826	921	4821	50.2%	1.03 [0.95 , 1.12]
Subtotal (95% CI)		**9036**		**8051**	**100.0%**	**1.05 [0.99 , 1.11]**
Total events:	2179		1658			
Heterogeneity: Tau² = 0.00; Chi² = 8.56, df = 9 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						



Analysis 2.19. Comparison 2: RotaTeq versus placebo, Outcome 19: Reactogenicity: vomiting

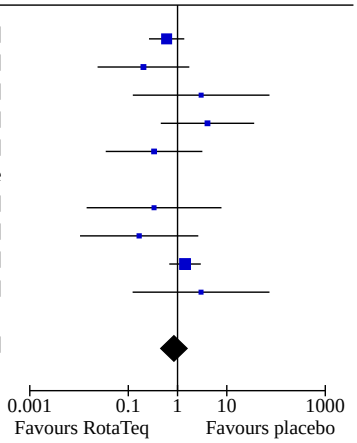
Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.19.1 After dose 1						
TEQ Clark 2003-USA	91	565	27	146	53.0%	0.87 [0.59 , 1.29]
TEQ Mo 2017-CHN	40	2015	49	2019	47.0%	0.82 [0.54 , 1.24]
Subtotal (95% CI)		**2580**		**2165**	**100.0%**	**0.85 [0.64 , 1.12]**
Total events:	131		76			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
2.19.2 After dose 2						
TEQ Mo 2017-CHN	11	1946	16	1959	100.0%	0.69 [0.32 , 1.49]
Subtotal (95% CI)		**1946**		**1959**	**100.0%**	**0.69 [0.32 , 1.49]**
Total events:	11		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
2.19.3 After dose 3						
TEQ Mo 2017-CHN	5	1932	11	1946	100.0%	0.46 [0.16 , 1.32]
Subtotal (95% CI)		**1932**		**1946**	**100.0%**	**0.46 [0.16 , 1.32]**
Total events:	5		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
2.19.4 End of follow-up						
TEQ Ciarlet 2009-EU	62	201	49	202	6.8%	1.27 [0.92 , 1.75]
TEQ Clark 2003-USA	171	573	41	148	8.3%	1.08 [0.81 , 1.44]
TEQ Clark 2004-USA	58	218	52	220	6.6%	1.13 [0.81 , 1.56]
TEQ Dhingra 2014-IND	4	20	5	20	0.5%	0.80 [0.25 , 2.55]
TEQ Iwata 2013-JPN	31	380	29	381	2.9%	1.07 [0.66 , 1.74]
TEQ Lawrence 2012-CHN	9	24	12	24	1.6%	0.75 [0.39 , 1.44]
TEQ Levin 2017-AF	18	99	16	103	1.8%	1.17 [0.63 , 2.16]
TEQ Mo 2017-CHN	54	2015	71	2019	5.7%	0.76 [0.54 , 1.08]
TEQ Vesikari 2006b-INT	618	4826	646	4821	65.7%	0.96 [0.86 , 1.06]
Subtotal (95% CI)		**8356**		**7938**	**100.0%**	**0.98 [0.91 , 1.07]**
Total events:	1025		921			
Heterogeneity: Tau² = 0.00; Chi² = 7.11, df = 8 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						



Analysis 2.20. Comparison 2: RotaTeq versus placebo, Outcome 20: Adverse events requiring discontinuation (end of follow-up)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
TEQ Armah 2010-AF	9	2733	15	2735	30.1%	0.60 [0.26 , 1.37]
TEQ Block 2007-EU/USA	1	650	5	660	7.3%	0.20 [0.02 , 1.73]
TEQ Ciarlet 2009-EU	1	201	0	202	3.5%	3.01 [0.12 , 73.57]
TEQ Clark 2004-USA	4	218	1	221	7.0%	4.06 [0.46 , 35.99]
TEQ Iwata 2013-JPN	1	381	3	381	6.6%	0.33 [0.03 , 3.19]
TEQ Kim 2008-KOR	0	115	0	63		Not estimable
TEQ Lawrence 2012-CHN	0	24	1	24	3.6%	0.33 [0.01 , 7.80]
TEQ Merck[009] 2005-USA	1	680	1	113	4.6%	0.17 [0.01 , 2.64]
TEQ Mo 2017-CHN	17	2015	12	2019	33.9%	1.42 [0.68 , 2.96]
TEQ Zaman 2010-AS	1	1018	0	1018	3.5%	3.00 [0.12 , 73.56]
Total (95% CI)		**8035**		**7436**	**100.0%**	**0.84 [0.46 , 1.56]**
Total events:	35		38			

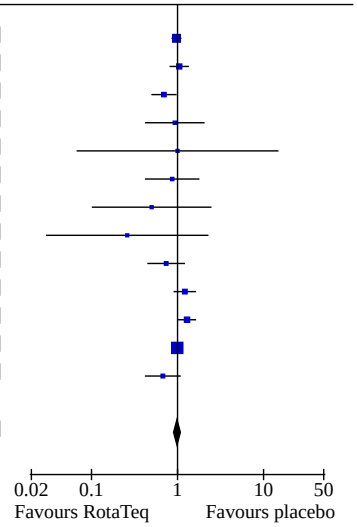
Heterogeneity: Tau² = 0.15; Chi² = 9.73, df = 8 (P = 0.28); I² = 18%
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable



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

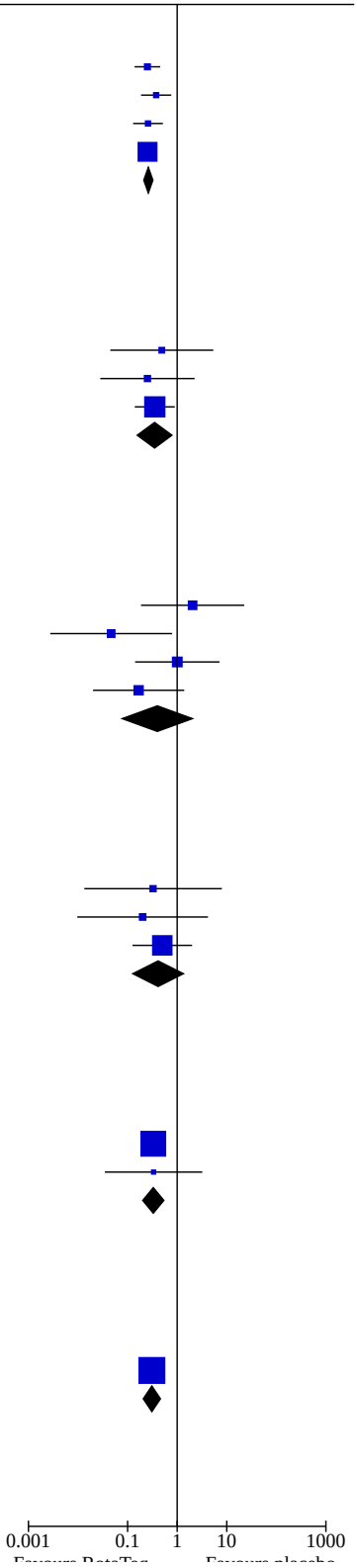
Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
TEQ Armah 2010-AF	376	2733	387	2735	21.2%	0.97 [0.85 , 1.11]
TEQ Block 2007-EU/USA	99	651	96	661	9.3%	1.05 [0.81 , 1.36]
TEQ Clark 2003-USA	97	581	36	150	6.0%	0.70 [0.50 , 0.98]
TEQ Clark 2004-USA	11	218	12	221	1.2%	0.93 [0.42 , 2.06]
TEQ Dhingra 2014-IND	1	20	1	20	0.1%	1.00 [0.07 , 14.90]
TEQ Iwata 2013-JPN	13	381	15	381	1.5%	0.87 [0.42 , 1.80]
TEQ Lawrence 2012-CHN	2	24	4	24	0.3%	0.50 [0.10 , 2.48]
TEQ Levin 2017-AF	1	99	4	103	0.2%	0.26 [0.03 , 2.29]
TEQ Merck[009] 2005-USA	71	680	16	113	3.0%	0.74 [0.45 , 1.22]
TEQ Mo 2017-CHN	90	2020	74	2020	7.3%	1.22 [0.90 , 1.64]
TEQ Vesikari 2006a-FIN	390	1624	60	322	10.1%	1.29 [1.01 , 1.65]
TEQ Vesikari 2006b-INT	5846	34035	5882	34003	36.6%	0.99 [0.96 , 1.03]
TEQ Zaman 2010-AS	27	1018	40	1018	3.2%	0.68 [0.42 , 1.09]
Total (95% CI)		**44084**		**41771**	**100.0%**	**0.98 [0.90 , 1.08]**
Total events:	7024		6627			

Heterogeneity: Tau² = 0.01; Chi² = 16.79, df = 12 (P = 0.16); I² = 29%
Test for overall effect: Z = 0.34 (P = 0.74)
Test for subgroup differences: Not applicable



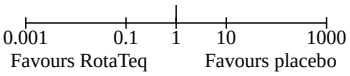
Analysis 2.22. Comparison 2: RotaTeq versus placebo, Outcome 22: Subgroup analysis: rotavirus diarrhoea of any severity (by G- or P-type)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.22.1 G1						
TEQ Block 2007-EU/USA	13	551	53	564	12.5%	0.25 [0.14 , 0.46]
TEQ Clark 2004-USA	10	187	26	183	9.0%	0.38 [0.19 , 0.76]
TEQ Mo 2017-CHN	10	1927	39	1937	9.3%	0.26 [0.13 , 0.51]
TEQ Vesikari 2006b-INT	72	2834	286	2839	69.2%	0.25 [0.20 , 0.32]
Subtotal (95% CI)		**5499**		**5523**	**100.0%**	**0.26 [0.21 , 0.32]**
Total events:	105		404			
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 3 (P = 0.77); I² = 0%						
Test for overall effect: Z = 12.47 (P < 0.00001)						
2.22.2 G2						
TEQ Clark 2004-USA	1	187	2	183	11.3%	0.49 [0.04 , 5.35]
TEQ Mo 2017-CHN	1	1927	4	1937	13.5%	0.25 [0.03 , 2.25]
TEQ Vesikari 2006b-INT	6	2834	17	2839	75.1%	0.35 [0.14 , 0.90]
Subtotal (95% CI)		**4948**		**4959**	**100.0%**	**0.35 [0.16 , 0.78]**
Total events:	8		23			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 2 (P = 0.92); I² = 0%						
Test for overall effect: Z = 2.55 (P = 0.01)						
2.22.3 G3						
TEQ Block 2007-EU/USA	2	551	1	564	24.0%	2.05 [0.19 , 22.51]
TEQ Clark 2004-USA	0	187	10	183	19.9%	0.05 [0.00 , 0.79]
TEQ Mo 2017-CHN	2	1927	2	1937	29.0%	1.01 [0.14 , 7.13]
TEQ Vesikari 2006b-INT	1	2834	6	2839	27.1%	0.17 [0.02 , 1.39]
Subtotal (95% CI)		**5499**		**5523**	**100.0%**	**0.40 [0.08 , 2.02]**
Total events:	5		19			
Heterogeneity: Tau² = 1.38; Chi² = 6.03, df = 3 (P = 0.11); I² = 50%						
Test for overall effect: Z = 1.11 (P = 0.27)						
2.22.4 G4						
TEQ Clark 2004-USA	0	187	1	183	13.5%	0.33 [0.01 , 7.96]
TEQ Mo 2017-CHN	0	1927	2	1937	14.9%	0.20 [0.01 , 4.18]
TEQ Vesikari 2006b-INT	3	2834	6	2839	71.6%	0.50 [0.13 , 2.00]
Subtotal (95% CI)		**4948**		**4959**	**100.0%**	**0.41 [0.13 , 1.33]**
Total events:	3		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
2.22.5 G9						
TEQ Mo 2017-CHN	20	1927	61	1937	95.3%	0.33 [0.20 , 0.54]
TEQ Vesikari 2006b-INT	1	2834	3	2839	4.7%	0.33 [0.03 , 3.21]
Subtotal (95% CI)		**4761**		**4776**	**100.0%**	**0.33 [0.20 , 0.54]**
Total events:	21		64			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 4.44 (P < 0.00001)						
2.22.6 P8						
TEQ Mo 2017-CHN (1)	31	1927	101	1937	100.0%	0.31 [0.21 , 0.46]
Subtotal (95% CI)		**1927**		**1937**	**100.0%**	**0.31 [0.21 , 0.46]**
Total events:	31		101			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.80 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.91, df = 5 (P = 0.86), I² = 0%						



Analysis 2.22. (Continued)

Test for subgroup differences: Chi² = 1.91, df = 5 (P = 0.86), I² = 0%

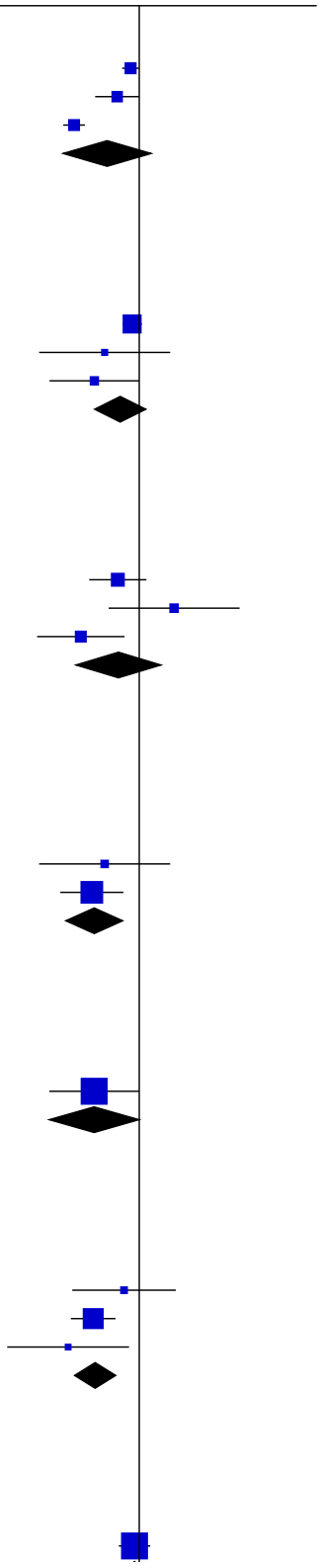


Footnotes

(1) P1A[8], not mutually exclusive with G1, G2, G3, G4, or G9

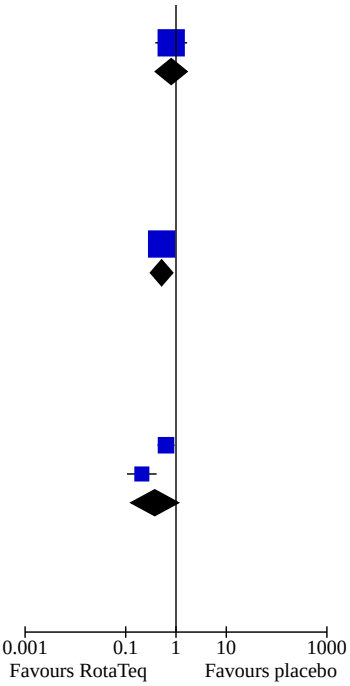
Analysis 2.23. Comparison 2: RotaTeq versus placebo, Outcome 23: Subgroup analysis: severe cases of rotavirus diarrhoea (by G- or P-type)

Study or Subgroup	RotaTeq Events	RotaTeq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.23.1 G1						
TEQ Armah 2010-AF	42	2016	62	1992	34.2%	0.67 [0.45 , 0.99]
TEQ Mo 2017-CHN	5	1926	14	1937	31.9%	0.36 [0.13 , 1.00]
TEQ Vesikari 2006b-INT	16	34035	328	34003	33.9%	0.05 [0.03 , 0.08]
Subtotal (95% CI)		**37977**		**37932**	**100.0%**	**0.23 [0.03 , 1.73]**
Total events:	63		404			
Heterogeneity: Tau² = 3.12; Chi² = 77.97, df = 2 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 1.43 (P = 0.15)						
2.23.2 G2						
TEQ Armah 2010-AF	32	2016	44	1992	65.0%	0.72 [0.46 , 1.13]
TEQ Mo 2017-CHN	0	1926	2	1937	12.6%	0.20 [0.01 , 4.19]
TEQ Vesikari 2006b-INT	1	34035	8	34003	22.4%	0.12 [0.02 , 1.00]
Subtotal (95% CI)		**37977**		**37932**	**100.0%**	**0.41 [0.13 , 1.35]**
Total events:	33		54			
Heterogeneity: Tau² = 0.51; Chi² = 3.26, df = 2 (P = 0.20); I² = 39%						
Test for overall effect: Z = 1.46 (P = 0.14)						
2.23.3 G3						
TEQ Armah 2010-AF	3	2016	8	1992	42.7%	0.37 [0.10 , 1.39]
TEQ Mo 2017-CHN	2	1926	0	1937	23.4%	5.03 [0.24 , 104.67]
TEQ Vesikari 2006b-INT	1	34035	15	34003	33.9%	0.07 [0.01 , 0.50]
Subtotal (95% CI)		**37977**		**37932**	**100.0%**	**0.38 [0.05 , 2.72]**
Total events:	6		23			
Heterogeneity: Tau² = 1.90; Chi² = 5.60, df = 2 (P = 0.06); I² = 64%						
Test for overall effect: Z = 0.96 (P = 0.34)						
2.23.4 G4						
TEQ Armah 2010-AF	0	2016	0	1992		Not estimable
TEQ Mo 2017-CHN	0	1926	2	1937	18.8%	0.20 [0.01 , 4.19]
TEQ Vesikari 2006b-INT	2	34035	18	34003	81.2%	0.11 [0.03 , 0.48]
Subtotal (95% CI)		**37977**		**37932**	**100.0%**	**0.12 [0.03 , 0.46]**
Total events:	2		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 3.11 (P = 0.002)						
2.23.5 G8						
TEQ Armah 2010-AF	1	2016	8	1992	100.0%	0.12 [0.02 , 0.99]
Subtotal (95% CI)		**2016**		**1992**	**100.0%**	**0.12 [0.02 , 0.99]**
Total events:	1		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
2.23.6 G9						
TEQ Armah 2010-AF	1	2016	2	1992	15.3%	0.49 [0.04 , 5.44]
TEQ Mo 2017-CHN	4	1926	34	1937	73.6%	0.12 [0.04 , 0.33]
TEQ Vesikari 2006b-INT	0	34035	13	34003	11.1%	0.04 [0.00 , 0.62]
Subtotal (95% CI)		**37977**		**37932**	**100.0%**	**0.13 [0.05 , 0.33]**
Total events:	5		49			
Heterogeneity: Tau² = 0.04; Chi² = 2.08, df = 2 (P = 0.35); I² = 4%						
Test for overall effect: Z = 4.21 (P < 0.0001)						
2.23.7 P4						
TEQ Armah 2010-AF	13	2016	16	1992	100.0%	0.80 [0.39 , 1.66]



Analysis 2.23. (Continued)

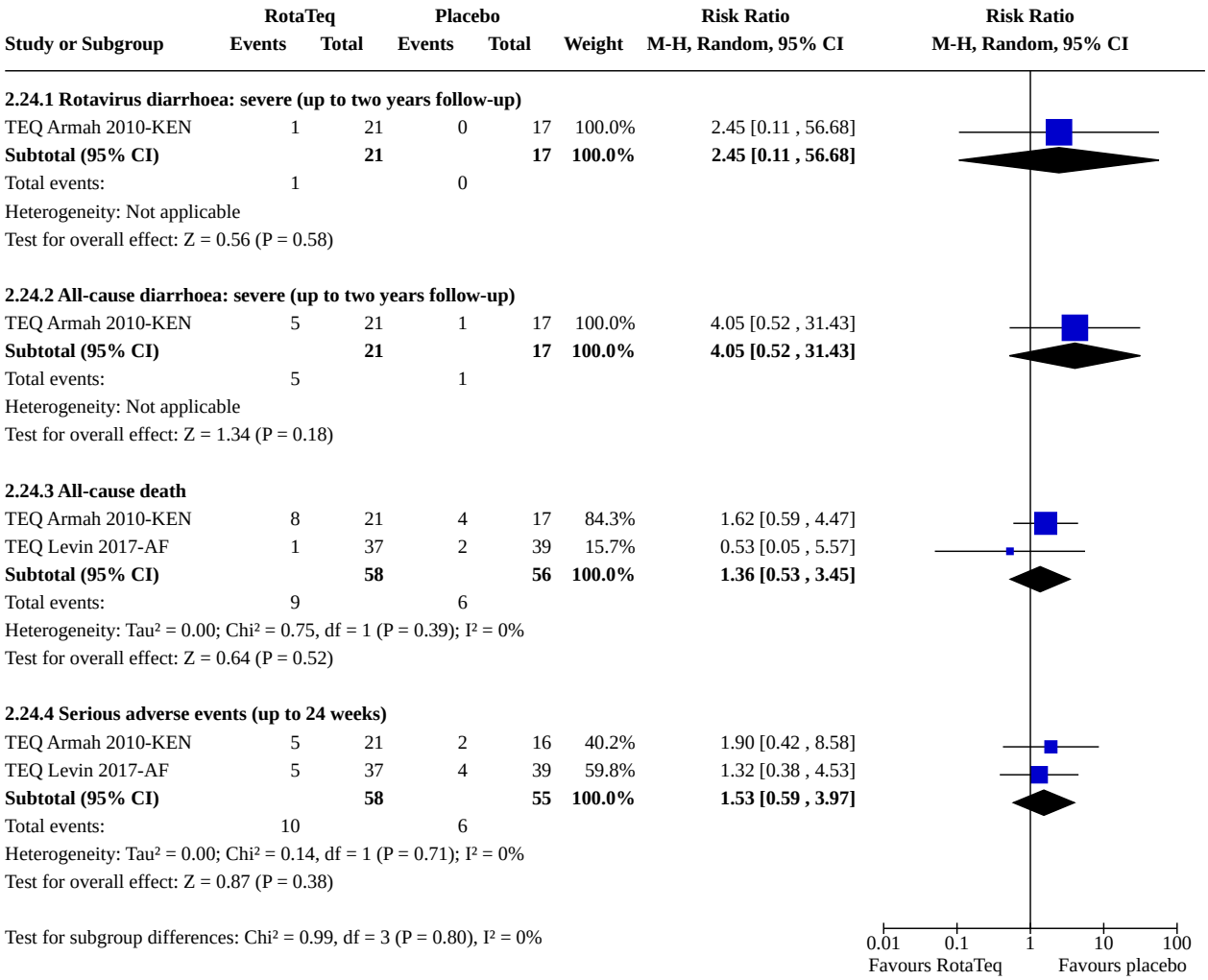
2.23.7 P4						
TEQ Armah 2010-AF	13	2016	16	1992	100.0%	0.80 [0.39 , 1.66]
Subtotal (95% CI)		**2016**		**1992**	**100.0%**	**0.80 [0.39 , 1.66]**
Total events:	13		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
2.23.8 P6						
TEQ Armah 2010-AF	22	2016	42	1992	100.0%	0.52 [0.31 , 0.86]
Subtotal (95% CI)		**2016**		**1992**	**100.0%**	**0.52 [0.31 , 0.86]**
Total events:	22		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.52 (P = 0.01)						
2.23.9 P8						
TEQ Armah 2010-AF	41	2016	64	1992	53.2%	0.63 [0.43 , 0.93]
TEQ Mo 2017-CHN (1)	10	1927	48	1937	46.8%	0.21 [0.11 , 0.41]
Subtotal (95% CI)		**3943**		**3929**	**100.0%**	**0.38 [0.13 , 1.12]**
Total events:	51		112			
Heterogeneity: Tau² = 0.54; Chi² = 7.84, df = 1 (P = 0.005); I² = 87%						
Test for overall effect: Z = 1.75 (P = 0.08)						



Footnotes

(1) P1A[8], not mutually exclusive with G1, G2, G3, G4, or G9

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



Comparison 3. Rotasiil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Rotavirus diarrhoea: severe (up to 1 year follow-up)	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.33, 0.81]
3.2 Rotavirus diarrhoea: severe (up to 2 years follow-up)	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.42, 0.74]
3.3 All-cause diarrhoea: severe cases (up to 1 year follow-up)	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.84, 1.01]
3.4 All-cause diarrhoea: severe cases (up to 2 years follow-up)	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.88, 1.01]
3.5 All-cause death	2	11586	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.82, 1.59]
3.6 All serious adverse events	3	11646	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.04]

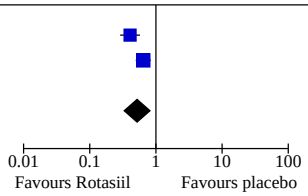
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7 Serious adverse events: intussusception	2	11586	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.35, 2.74]
3.8 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.59, 0.76]
3.9 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.71, 0.84]
3.10 Rotavirus diarrhoea: requiring hospitalization	1	15000	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.52, 0.79]
3.10.1 Up to 1 year follow-up	1	7500	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.39, 0.88]
3.10.2 Up to 2 years follow-up	1	7500	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.52, 0.85]
3.11 All-cause diarrhoea: of any severity (up to 1 year follow-up)	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.04]
3.12 All-cause diarrhoea: of any severity (up to 2 years follow-up)	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.02]
3.13 Reactogenicity: fever	4	5217	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
3.13.1 After any dose	4	5217	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
3.14 Reactogenicity: diarrhoea	4	5217	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.58, 1.16]
3.14.1 After any dose	4	5217	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.58, 1.16]
3.15 Reactogenicity: vomiting	4	5217	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.13]
3.15.1 After any dose	4	5217	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.13]
3.16 Adverse events requiring discontinuation	1	7500	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.17 Dropouts before the end of the trial	2	11591	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.66, 1.32]
3.18 Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 2 years follow-up)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.18.1 G1	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.24, 1.03]
3.18.2 G2	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.34, 0.76]
3.18.3 G3	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.11, 2.19]
3.18.4 G4	1	3508	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.18.5 G8	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.94]
3.18.6 G9	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.53, 1.02]
3.18.7 G12	2	11008	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.45, 1.36]
3.18.8 P4	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.28, 0.65]
3.18.9 P6	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.45]
3.18.10 P8	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.45, 1.67]
3.19 Subgroup analysis: rotavirus diarrhoea of any severity by G and P types (up to 2 years follow-up)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.19.1 G1	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.39, 0.97]
3.19.2 G2	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.52, 0.82]
3.19.3 G3	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.31, 1.56]
3.19.4 G4	1	3508	Risk Ratio (M-H, Random, 95% CI)	2.91 [0.12, 71.44]
3.19.5 G8	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.94]
3.19.6 G9	1	3508	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.67, 1.81]
3.19.7 G12	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.47]
3.19.8 P4	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.53, 0.84]
3.19.9 P6	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.96]
3.19.10 P8	1	3508	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.61, 1.20]

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

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	44	1780	105	1728	46.8%	0.41 [0.29 , 0.57]
SIIL Kulkarni 2017-IND	90	3749	140	3751	53.2%	0.64 [0.50 , 0.83]
Total (95% CI)		**5529**		**5479**	**100.0%**	**0.52 [0.33 , 0.81]**
Total events:	134		245			

Heterogeneity: Tau² = 0.08; Chi² = 4.30, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 2.87 (P = 0.004)
Test for subgroup differences: Not applicable

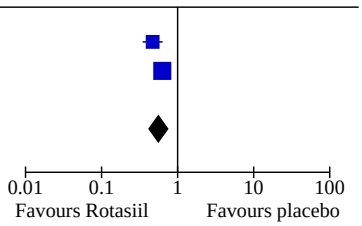


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

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

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	59	1780	122	1728	40.8%	0.47 [0.35 , 0.64]
SIIL Kulkarni 2017-IND	186	3749	296	3751	59.2%	0.63 [0.53 , 0.75]
Total (95% CI)		**5529**		**5479**	**100.0%**	**0.56 [0.42 , 0.74]**
Total events:	245		418			

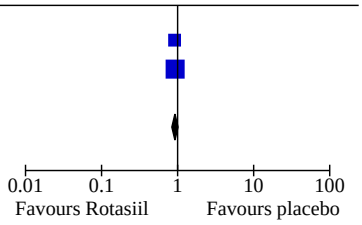
Heterogeneity: Tau² = 0.03; Chi² = 2.65, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 4.06 (P < 0.0001)
Test for subgroup differences: Not applicable



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

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	266	1780	283	1728	36.6%	0.91 [0.78 , 1.06]
SIIL Kulkarni 2017-IND	472	3749	509	3751	63.4%	0.93 [0.83 , 1.04]
Total (95% CI)		**5529**		**5479**	**100.0%**	**0.92 [0.84 , 1.01]**
Total events:	738		792			

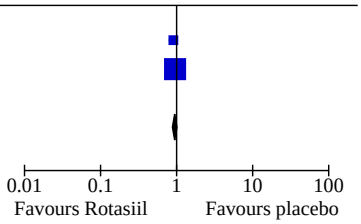
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Rotasiil versus placebo, Outcome 4: All-cause diarrhoea: severe cases (up to 2 years follow-up)

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	311	1780	333	1728	23.5%	0.91 [0.79 , 1.04]
SIIL Kulkarni 2017-IND	934	3749	979	3751	76.5%	0.95 [0.88 , 1.03]
Total (95% CI)		**5529**		**5479**	**100.0%**	**0.94 [0.88 , 1.01]**
Total events:	1245		1312			

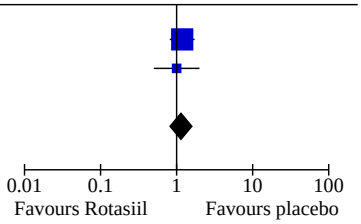
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Rotasiil versus placebo, Outcome 5: All-cause death

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	58	2042	49	2044	77.2%	1.18 [0.81 , 1.72]
SIIL Kulkarni 2017-IND	16	3749	16	3751	22.8%	1.00 [0.50 , 2.00]
Total (95% CI)		**5791**		**5795**	**100.0%**	**1.14 [0.82 , 1.59]**
Total events:	74		65			

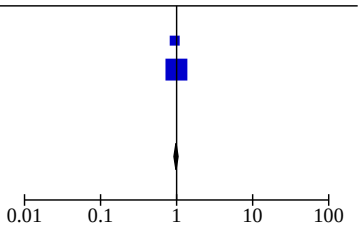
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Rotasiil versus placebo, Outcome 6: All serious adverse events

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	395	2042	419	2044	24.3%	0.94 [0.83 , 1.07]
SIIL Kulkarni 2017-IND	1109	3749	1116	3751	75.7%	0.99 [0.93 , 1.07]
SIIL Zade 2014-INDc	0	30	0	30		Not estimable
Total (95% CI)		**5821**		**5825**	**100.0%**	**0.98 [0.92 , 1.04]**
Total events:	1504		1535			

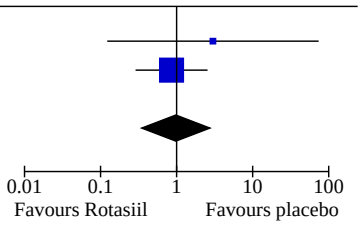
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Rotasiil versus placebo, Outcome 7: Serious adverse events: intussusception

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	1	2042	0	2044	10.4%	3.00 [0.12 , 73.67]
SIIL Kulkarni 2017-IND	6	3749	7	3751	89.6%	0.86 [0.29 , 2.55]
Total (95% CI)		**5791**		**5795**	**100.0%**	**0.98 [0.35 , 2.74]**
Total events:	7		7			

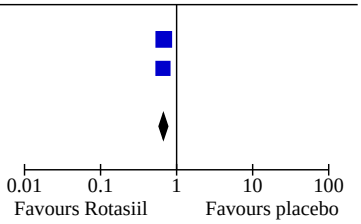
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.96)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Rotasiil versus placebo, Outcome 8: Rotavirus diarrhoea: of any severity (up to 1 year follow-up)

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	176	1780	252	1728	53.3%	0.68 [0.57 , 0.81]
SIIL Kulkarni 2017-IND	162	3749	245	3751	46.7%	0.66 [0.55 , 0.80]
Total (95% CI)		**5529**		**5479**	**100.0%**	**0.67 [0.59 , 0.76]**
Total events:	338		497			

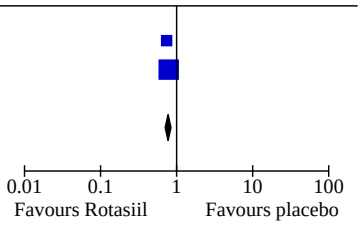
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 5.94 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Rotasiil versus placebo, Outcome 9: Rotavirus diarrhoea: of any severity (up to 2 years follow-up)

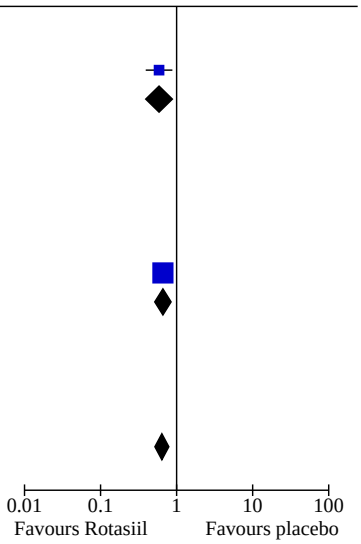
Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	233	1780	306	1728	30.6%	0.74 [0.63 , 0.86]
SIIL Kulkarni 2017-IND	531	3749	675	3751	69.4%	0.79 [0.71 , 0.87]
Total (95% CI)		**5529**		**5479**	**100.0%**	**0.77 [0.71 , 0.84]**
Total events:	764		981			

Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 5.83 (P < 0.00001)
Test for subgroup differences: Not applicable



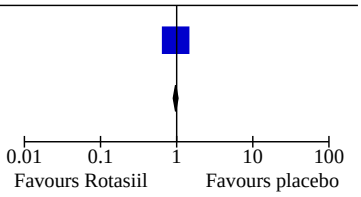
Analysis 3.10. Comparison 3: Rotasiil versus placebo, Outcome 10: Rotavirus diarrhoea: requiring hospitalization

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.10.1 Up to 1 year follow-up						
SIIL Kulkarni 2017-IND	37	3749	63	3751	27.3%	0.59 [0.39 , 0.88]
Subtotal (95% CI)		**3749**		**3751**	**27.3%**	**0.59 [0.39 , 0.88]**
Total events:	37		63			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.58 (P = 0.010)						
3.10.2 Up to 2 years follow-up						
SIIL Kulkarni 2017-IND	101	3749	153	3751	72.7%	0.66 [0.52 , 0.85]
Subtotal (95% CI)		**3749**		**3751**	**72.7%**	**0.66 [0.52 , 0.85]**
Total events:	101		153			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.29 (P = 0.001)						
Total (95% CI)		**7498**		**7502**	**100.0%**	**0.64 [0.52 , 0.79]**
Total events:	138		216			
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 4.15 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						



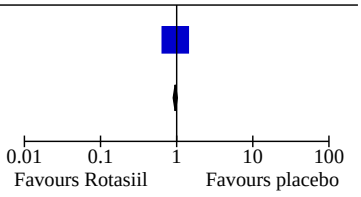
Analysis 3.11. Comparison 3: Rotasiil versus placebo, Outcome 11: All-cause diarrhoea: of any severity (up to 1 year follow-up)

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	834	1780	835	1728	100.0%	0.97 [0.90 , 1.04]
Total (95% CI)		**1780**		**1728**	**100.0%**	**0.97 [0.90 , 1.04]**
Total events:	834		835			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.38)						
Test for subgroup differences: Not applicable						



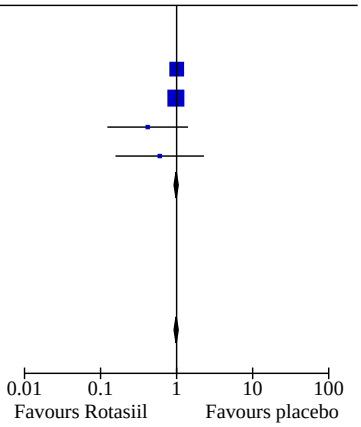
Analysis 3.12. Comparison 3: Rotasiil versus placebo, Outcome 12: All-cause diarrhoea: of any severity (up to 2 years follow-up)

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	958	1780	970	1728	100.0%	0.96 [0.90 , 1.02]
Total (95% CI)		**1780**		**1728**	**100.0%**	**0.96 [0.90 , 1.02]**
Total events:	958		970			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						
Test for subgroup differences: Not applicable						



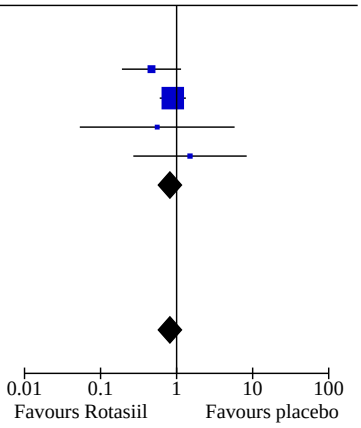
Analysis 3.13. Comparison 3: Rotasiil versus placebo, Outcome 13: Reactogenicity: fever

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.13.1 After any dose						
SIIL Isanaka 2017-NER	636	2044	635	2047	44.9%	1.00 [0.92 , 1.10]
SIIL Kulkarni 2017-IND	341	500	355	509	54.6%	0.98 [0.90 , 1.06]
SIIL Zade 2014-INDb	3	27	8	30	0.3%	0.42 [0.12 , 1.41]
SIIL Zade 2014-INDc	3	30	5	30	0.2%	0.60 [0.16 , 2.29]
Subtotal (95% CI)		**2601**		**2616**	**100.0%**	**0.99 [0.93 , 1.05]**
Total events:	983		1003			
Heterogeneity: Tau² = 0.00; Chi² = 2.62, df = 3 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Total (95% CI)		**2601**		**2616**	**100.0%**	**0.99 [0.93 , 1.05]**
Total events:	983		1003			
Heterogeneity: Tau² = 0.00; Chi² = 2.62, df = 3 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: Not applicable						



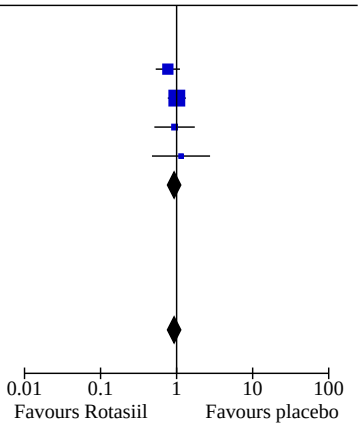
Analysis 3.14. Comparison 3: Rotasiil versus placebo, Outcome 14: Reactogenicity: diarrhoea

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.14.1 After any dose						
SIIL Isanaka 2017-NER	7	2044	15	2047	15.3%	0.47 [0.19 , 1.14]
SIIL Kulkarni 2017-IND	42	500	48	509	78.3%	0.89 [0.60 , 1.32]
SIIL Zade 2014-INDb	1	27	2	30	2.2%	0.56 [0.05 , 5.79]
SIIL Zade 2014-INDc	3	30	2	30	4.2%	1.50 [0.27 , 8.34]
Subtotal (95% CI)		**2601**		**2616**	**100.0%**	**0.82 [0.58 , 1.16]**
Total events:	53		67			
Heterogeneity: Tau² = 0.00; Chi² = 2.27, df = 3 (P = 0.52); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.26)						
Total (95% CI)		**2601**		**2616**	**100.0%**	**0.82 [0.58 , 1.16]**
Total events:	53		67			
Heterogeneity: Tau² = 0.00; Chi² = 2.27, df = 3 (P = 0.52); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.26)						
Test for subgroup differences: Not applicable						



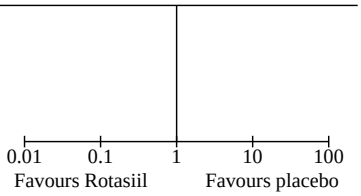
Analysis 3.15. Comparison 3: Rotasiil versus placebo, Outcome 15: Reactogenicity: vomiting

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.15.1 After any dose						
SIIL Isanaka 2017-NER	49	2044	64	2047	30.0%	0.77 [0.53 , 1.11]
SIIL Kulkarni 2017-IND	85	500	86	509	54.1%	1.01 [0.77 , 1.32]
SIIL Zade 2014-INDb	11	27	13	30	10.8%	0.94 [0.51 , 1.73]
SIIL Zade 2014-INDc	8	30	7	30	5.2%	1.14 [0.47 , 2.75]
Subtotal (95% CI)		**2601**		**2616**	**100.0%**	**0.93 [0.76 , 1.13]**
Total events:	153		170			
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 3 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)		**2601**		**2616**	**100.0%**	**0.93 [0.76 , 1.13]**
Total events:	153		170			
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 3 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Test for subgroup differences: Not applicable						



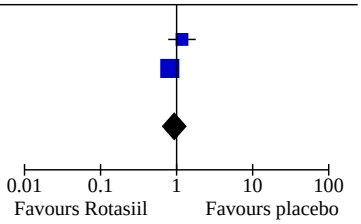
Analysis 3.16. Comparison 3: Rotasiil versus placebo, Outcome 16: Adverse events requiring discontinuation

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Kulkarni 2017-IND	0	3749	0	3751		Not estimable
Total (95% CI)		**3749**		**3751**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



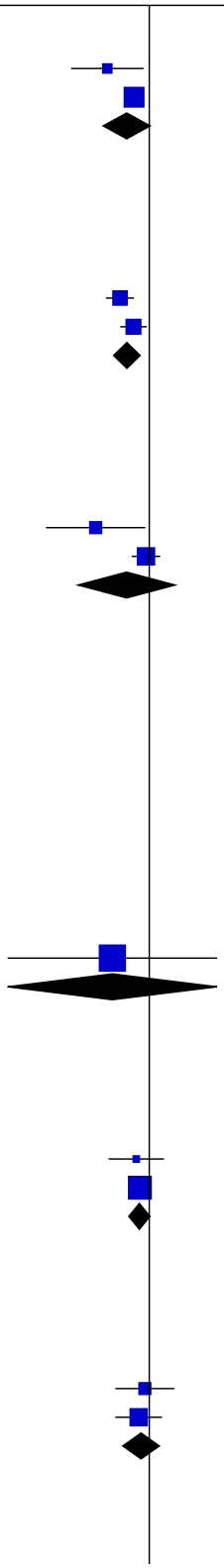
Analysis 3.17. Comparison 3: Rotasiil versus placebo, Outcome 17: Dropouts before the end of the trial

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SIIL Isanaka 2017-NER	47	2044	40	2047	36.4%	1.18 [0.78 , 1.79]
SIIL Kulkarni 2017-IND	209	3749	257	3751	63.6%	0.81 [0.68 , 0.97]
Total (95% CI)		**5793**		**5798**	**100.0%**	**0.93 [0.66 , 1.32]**
Total events:	256		297			
Heterogeneity: Tau² = 0.04; Chi² = 2.55, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 0.41 (P = 0.68)						
Test for subgroup differences: Not applicable						



Analysis 3.18. Comparison 3: Rotasiil versus placebo, Outcome 18: Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 2 years follow-up)

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.18.1 G1						
SIIL Isanaka 2017-NER	4	1780	14	1728	27.6%	0.28 [0.09 , 0.84]
SIIL Kulkarni 2017-IND	81	3749	129	3751	72.4%	0.63 [0.48 , 0.83]
Subtotal (95% CI)		**5529**		**5479**	**100.0%**	**0.50 [0.24 , 1.03]**
Total events:	85		143			
Heterogeneity: Tau² = 0.17; Chi² = 1.97, df = 1 (P = 0.16); I² = 49%						
Test for overall effect: Z = 1.89 (P = 0.06)						
3.18.2 G2						
SIIL Isanaka 2017-NER	29	1780	69	1728	48.6%	0.41 [0.27 , 0.63]
SIIL Kulkarni 2017-IND	37	3749	60	3751	51.4%	0.62 [0.41 , 0.93]
Subtotal (95% CI)		**5529**		**5479**	**100.0%**	**0.50 [0.34 , 0.76]**
Total events:	66		129			
Heterogeneity: Tau² = 0.04; Chi² = 1.88, df = 1 (P = 0.17); I² = 47%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
3.18.3 G3						
SIIL Isanaka 2017-NER	2	1780	10	1728	38.6%	0.19 [0.04 , 0.88]
SIIL Kulkarni 2017-IND	38	3749	42	3751	61.4%	0.91 [0.59 , 1.40]
Subtotal (95% CI)		**5529**		**5479**	**100.0%**	**0.50 [0.11 , 2.19]**
Total events:	40		52			
Heterogeneity: Tau² = 0.88; Chi² = 3.71, df = 1 (P = 0.05); I² = 73%						
Test for overall effect: Z = 0.92 (P = 0.36)						
3.18.4 G4						
SIIL Isanaka 2017-NER	0	1780	0	1728		Not estimable
Subtotal (95% CI)		**1780**		**1728**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.18.5 G8						
SIIL Isanaka 2017-NER	0	1780	1	1728	100.0%	0.32 [0.01 , 7.94]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.32 [0.01 , 7.94]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
3.18.6 G9						
SIIL Isanaka 2017-NER	9	1780	13	1728	14.6%	0.67 [0.29 , 1.57]
SIIL Kulkarni 2017-IND	54	3749	72	3751	85.4%	0.75 [0.53 , 1.06]
Subtotal (95% CI)		**5529**		**5479**	**100.0%**	**0.74 [0.53 , 1.02]**
Total events:	63		85			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.84 (P = 0.07)						
3.18.7 G12						
SIIL Isanaka 2017-NER	9	1780	10	1728	38.6%	0.87 [0.36 , 2.14]
SIIL Kulkarni 2017-IND	13	3749	18	3751	61.4%	0.72 [0.35 , 1.47]
Subtotal (95% CI)		**5529**		**5479**	**100.0%**	**0.78 [0.45 , 1.36]**
Total events:	22		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						



Analysis 3.18. (Continued)

Test for overall effect: Z = 0.88 (P = 0.38)

3.18.8 P4

SIIL Isanaka 2017-NER	31	1780	70	1728	100.0%	0.43 [0.28 , 0.65]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.43 [0.28 , 0.65]**
Total events:	31		70			

Heterogeneity: Not applicable

Test for overall effect: Z = 3.96 (P < 0.0001)

3.18.9 P6

SIIL Isanaka 2017-NER	6	1780	31	1728	100.0%	0.19 [0.08 , 0.45]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.19 [0.08 , 0.45]**
Total events:	6		31			

Heterogeneity: Not applicable

Test for overall effect: Z = 3.76 (P = 0.0002)

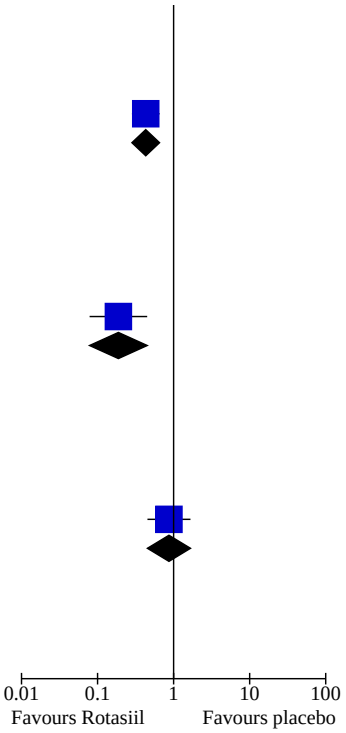
3.18.10 P8

SIIL Isanaka 2017-NER	17	1780	19	1728	100.0%	0.87 [0.45 , 1.67]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.87 [0.45 , 1.67]**
Total events:	17		19			

Heterogeneity: Not applicable

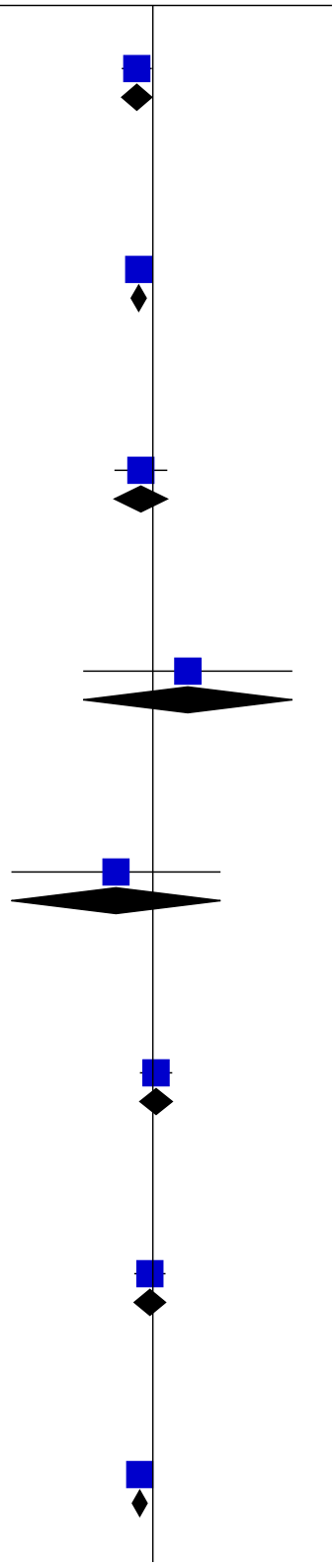
Test for overall effect: Z = 0.42 (P = 0.67)

Test for subgroup differences: $Chi^2 = 13.85$, df = 8 (P = 0.09), $I^2 = 42.2\%$



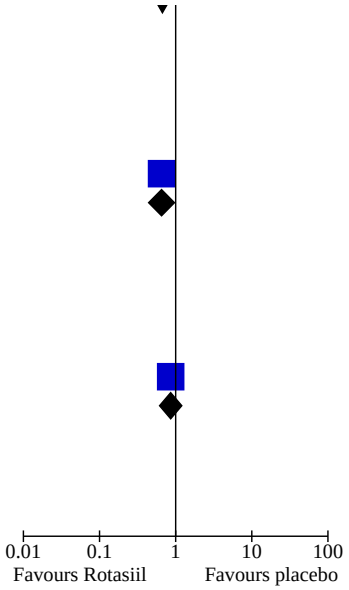
Analysis 3.19. Comparison 3: Rotasiil versus placebo, Outcome 19: Subgroup analysis: rotavirus diarrhoea of any severity by G and P types (up to 2 years follow-up)

Study or Subgroup	Rotasiil Events	Rotasiil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.19.1 G1						
SIIL Isanaka 2017-NER	29	1780	46	1728	100.0%	0.61 [0.39 , 0.97]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.61 [0.39 , 0.97]**
Total events:	29		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.09 (P = 0.04)						
3.19.2 G2						
SIIL Isanaka 2017-NER	113	1780	169	1728	100.0%	0.65 [0.52 , 0.82]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.65 [0.52 , 0.82]**
Total events:	113		169			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.70 (P = 0.0002)						
3.19.3 G3						
SIIL Isanaka 2017-NER	10	1780	14	1728	100.0%	0.69 [0.31 , 1.56]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.69 [0.31 , 1.56]**
Total events:	10		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
3.19.4 G4						
SIIL Isanaka 2017-NER	1	1780	0	1728	100.0%	2.91 [0.12 , 71.44]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**2.91 [0.12 , 71.44]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
3.19.5 G8						
SIIL Isanaka 2017-NER	0	1780	1	1728	100.0%	0.32 [0.01 , 7.94]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.32 [0.01 , 7.94]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
3.19.6 G9						
SIIL Isanaka 2017-NER	33	1780	29	1728	100.0%	1.10 [0.67 , 1.81]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**1.10 [0.67 , 1.81]**
Total events:	33		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.69)						
3.19.7 G12						
SIIL Isanaka 2017-NER	32	1780	34	1728	100.0%	0.91 [0.57 , 1.47]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.91 [0.57 , 1.47]**
Total events:	32		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
3.19.8 P4						
SIIL Isanaka 2017-NER	118	1780	171	1728	100.0%	0.67 [0.53 , 0.84]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.67 [0.53 , 0.84]**
Total events:	118		171			
Heterogeneity: Not applicable						



Analysis 3.19. (Continued)

Total events:	118		171			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.49 (P = 0.0005)						
3.19.9 P6						
SIIL Isanaka 2017-NER	41	1780	61	1728	100.0%	0.65 [0.44 , 0.96]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.65 [0.44 , 0.96]**
Total events:	41		61			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.14 (P = 0.03)						
3.19.10 P8						
SIIL Isanaka 2017-NER	62	1780	70	1728	100.0%	0.86 [0.61 , 1.20]
Subtotal (95% CI)		**1780**		**1728**	**100.0%**	**0.86 [0.61 , 1.20]**
Total events:	62		70			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
Test for subgroup differences: Chi² = 7.79, df = 9 (P = 0.56), I² = 0%						



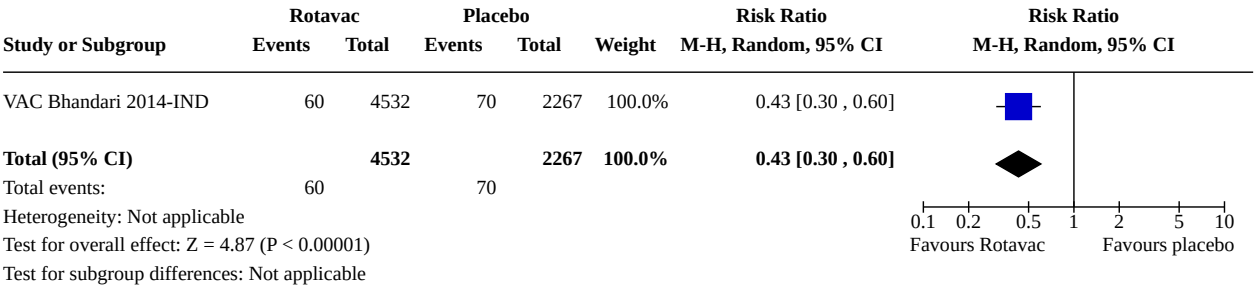
Comparison 4. Rotavac versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Rotavirus diarrhoea: severe (up to 1 year follow-up)	1	6799	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.30, 0.60]
4.2 Rotavirus diarrhoea: severe (2nd year of life)	1	6516	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.33, 0.81]
4.3 Rotavirus diarrhoea: severe (up to 2 years follow-up)	1	6541	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.35, 0.60]
4.4 All-cause diarrhoea: severe cases (up to 1 year follow-up)	1	6799	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.71, 0.98]
4.5 All-cause death	2	8155	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.50, 1.56]
4.6 All serious adverse events	3	8210	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.85, 1.02]
4.7 Serious adverse events: intussusception	4	8582	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.35, 5.02]
4.8 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)	1	6799	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.56, 0.78]
4.9 Rotavirus diarrhoea: of any severity (2nd year of life)	1	6516	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.53, 0.80]
4.10 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)	1	6541	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.57, 0.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.11 Rotavirus diarrhoea: requiring medical attention	1	6799	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.58, 0.81]
4.11.1 Up to 1 year follow-up (at least 1 rotavirus season)	1	6799	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.58, 0.81]
4.12 Reactogenicity: fever	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.12.1 After dose 1	2	427	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.34, 1.95]
4.12.2 After dose 2	1	356	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.33, 1.77]
4.12.3 After dose 3	1	358	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.52, 2.36]
4.13 Reactogenicity: diarrhoea	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.13.1 After dose 1	2	427	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.61, 1.30]
4.13.2 After dose 2	1	356	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.00, 2.41]
4.13.3 After dose 3	1	358	Risk Ratio (M-H, Random, 95% CI)	4.09 [2.11, 7.92]
4.14 Reactogenicity: vomiting	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.14.1 After dose 1	2	427	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.70, 2.55]
4.14.2 After dose 2	1	356	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.64, 3.66]
4.14.3 After dose 3	1	358	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.39, 2.66]
4.15 Dropouts before the end of the trial	3	8215	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.57, 1.29]
4.16 Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 1 year follow-up)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.16.1 G1P[8]	1	6541	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.36, 1.20]
4.16.2 G2P[4]	1	6541	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.22, 0.69]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.16.3 G12P[6]	1	6541	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.13, 0.74]
4.16.4 G12P[8]	1	6541	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.07, 1.26]
4.17 Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 2 years follow-up)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.17.1 G1P[8]	1	6541	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.38, 0.93]
4.17.2 G2P[4]	1	6541	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.62]
4.17.3 G9P[4]	1	6541	Risk Ratio (M-H, Random, 95% CI)	4.52 [0.57, 35.66]
4.17.4 G12P[6]	1	6541	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.13, 0.74]
4.17.5 G12P[8]	1	6541	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.10, 0.96]

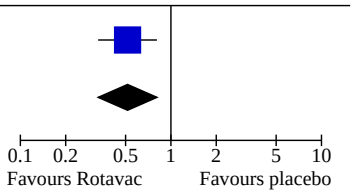
Analysis 4.1. Comparison 4: Rotavac versus placebo, Outcome 1: Rotavirus diarrhoea: severe (up to 1 year follow-up)



Analysis 4.2. Comparison 4: Rotavac versus placebo, Outcome 2: Rotavirus diarrhoea: severe (2nd year of life)

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VAC Bhandari 2014-IND	38	4339	37	2177	100.0%	0.52 [0.33 , 0.81]
Total (95% CI)		**4339**		**2177**	**100.0%**	**0.52 [0.33 , 0.81]**
Total events:	38		37			

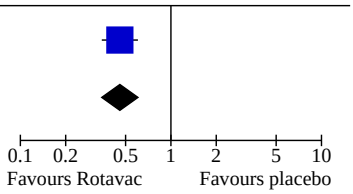
Heterogeneity: Not applicable
Test for overall effect: Z = 2.89 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Rotavac versus placebo, Outcome 3: Rotavirus diarrhoea: severe (up to 2 years follow-up)

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VAC Bhandari 2014-IND	93	4354	102	2187	100.0%	0.46 [0.35 , 0.60]
Total (95% CI)		**4354**		**2187**	**100.0%**	**0.46 [0.35 , 0.60]**
Total events:	93		102			

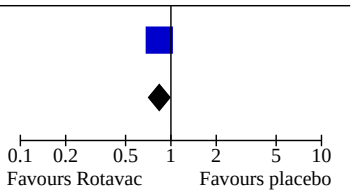
Heterogeneity: Not applicable
Test for overall effect: Z = 5.54 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Rotavac versus placebo, Outcome 4: All-cause diarrhoea: severe cases (up to 1 year follow-up)

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VAC Bhandari 2014-IND	353	4532	211	2267	100.0%	0.84 [0.71 , 0.98]
Total (95% CI)		**4532**		**2267**	**100.0%**	**0.84 [0.71 , 0.98]**
Total events:	353		211			

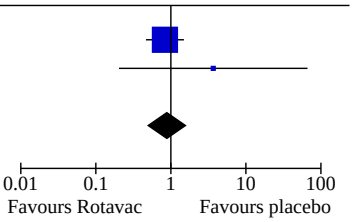
Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4: Rotavac versus placebo, Outcome 5: All-cause death

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VAC Bhandari 2014-IND	30	4532	18	2267	96.1%	0.83 [0.47 , 1.49]
VAC Chandola 2017-IND	5	1017	0	339	3.9%	3.67 [0.20 , 66.27]
Total (95% CI)		**5549**		**2606**	**100.0%**	**0.88 [0.50 , 1.56]**
Total events:	35		18			

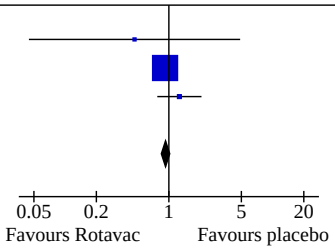
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 4.6. Comparison 4: Rotavac versus placebo, Outcome 6: All serious adverse events

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VAC Bhandari 2006-IND (1)	1	30	2	28	0.2%	0.47 [0.04 , 4.87]
VAC Bhandari 2014-IND	947	4531	515	2265	96.3%	0.92 [0.84 , 1.01]
VAC Chandola 2017-IND	72	1017	19	339	3.6%	1.26 [0.77 , 2.06]
Total (95% CI)		**5578**		**2632**	**100.0%**	**0.93 [0.85 , 1.02]**
Total events:	1020		536			

Heterogeneity: Tau² = 0.00; Chi² = 1.89, df = 2 (P = 0.39); I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable

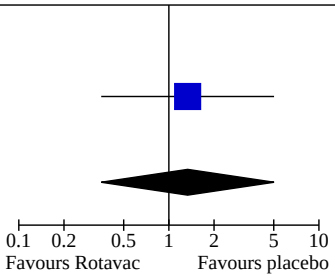


Footnotes
(1) intervention: 1 dose only

Analysis 4.7. Comparison 4: Rotavac versus placebo, Outcome 7: Serious adverse events: intussusception

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VAC Bhandari 2006-IND (1)	0	30	0	28		Not estimable
VAC Bhandari 2009-IND (2)	0	185	0	184		Not estimable
VAC Bhandari 2014-IND	8	4532	3	2267	100.0%	1.33 [0.35 , 5.02]
VAC Chandola 2017-IND	0	1017	0	339		Not estimable
Total (95% CI)		**5764**		**2818**	**100.0%**	**1.33 [0.35 , 5.02]**
Total events:	8		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable

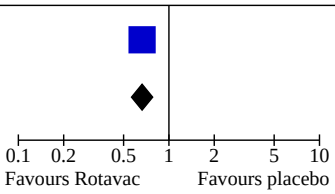


Footnotes
(1) intervention: 1 dose only
(2) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

Analysis 4.8. Comparison 4: Rotavac versus placebo, Outcome 8: Rotavirus diarrhoea: of any severity (up to 1 year follow-up)

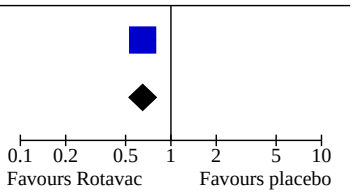
Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VAC Bhandari 2014-IND	313	4532	236	2267	100.0%	0.66 [0.56 , 0.78]
Total (95% CI)		**4532**		**2267**	**100.0%**	**0.66 [0.56 , 0.78]**
Total events:	313		236			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.99 (P < 0.00001)
Test for subgroup differences: Not applicable



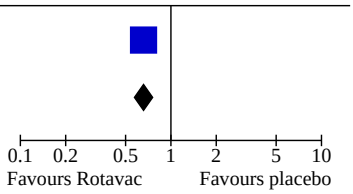
Analysis 4.9. Comparison 4: Rotavac versus placebo, Outcome 9: Rotavirus diarrhoea: of any severity (2nd year of life)

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VAC Bhandari 2014-IND	194	4339	150	2177	100.0%	0.65 [0.53 , 0.80]
Total (95% CI)		**4339**		**2177**	**100.0%**	**0.65 [0.53 , 0.80]**
Total events:	194		150			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.10 (P < 0.0001)						
Test for subgroup differences: Not applicable						



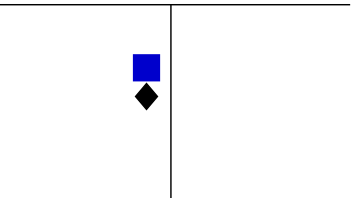
Analysis 4.10. Comparison 4: Rotavac versus placebo, Outcome 10: Rotavirus diarrhoea: of any severity (up to 2 years follow-up)

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VAC Bhandari 2014-IND	406	4354	310	2187	100.0%	0.66 [0.57 , 0.76]
Total (95% CI)		**4354**		**2187**	**100.0%**	**0.66 [0.57 , 0.76]**
Total events:	406		310			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.92 (P < 0.00001)						
Test for subgroup differences: Not applicable						



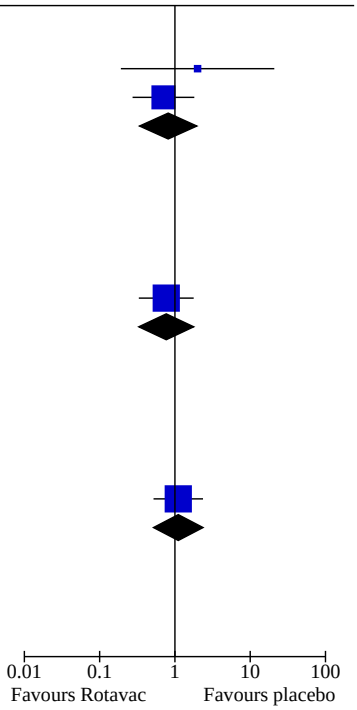
Analysis 4.11. Comparison 4: Rotavac versus placebo, Outcome 11: Rotavirus diarrhoea: requiring medical attention

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.11.1 Up to 1 year follow-up (at least 1 rotavirus season)						
VAC Bhandari 2014-IND	300	4532	218	2267	100.0%	0.69 [0.58 , 0.81]
Subtotal (95% CI)		**4532**		**2267**	**100.0%**	**0.69 [0.58 , 0.81]**
Total events:	300		218			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.38 (P < 0.0001)						
Total (95% CI)		**4532**		**2267**	**100.0%**	**0.69 [0.58 , 0.81]**
Total events:	300		218			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.38 (P < 0.0001)						
Test for subgroup differences: Not applicable						



Analysis 4.12. Comparison 4: Rotavac versus placebo, Outcome 12: Reactogenicity: fever

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.12.1 After dose 1						
VAC Bhandari 2006-IND (1)	2	30	1	30	13.9%	2.00 [0.19 , 20.90]
VAC Bhandari 2009-IND (2)	7	183	10	184	86.1%	0.70 [0.27 , 1.81]
Subtotal (95% CI)		**213**		**214**	**100.0%**	**0.81 [0.34 , 1.95]**
Total events:	9		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.65)						
4.12.2 After dose 2						
VAC Bhandari 2009-IND (2)	9	176	12	180	100.0%	0.77 [0.33 , 1.77]
Subtotal (95% CI)		**176**		**180**	**100.0%**	**0.77 [0.33 , 1.77]**
Total events:	9		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
4.12.3 After dose 3						
VAC Bhandari 2009-IND (2)	13	177	12	181	100.0%	1.11 [0.52 , 2.36]
Subtotal (95% CI)		**177**		**181**	**100.0%**	**1.11 [0.52 , 2.36]**
Total events:	13		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						



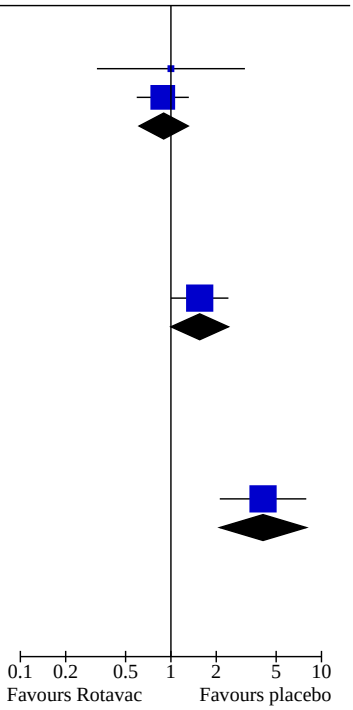
Footnotes

(1) intervention: 1 dose only

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

Analysis 4.13. Comparison 4: Rotavac versus placebo, Outcome 13: Reactogenicity: diarrhoea

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.13.1 After dose 1						
VAC Bhandari 2006-IND (1)	5	30	5	30	11.0%	1.00 [0.32 , 3.10]
VAC Bhandari 2009-IND (2)	36	183	41	184	89.0%	0.88 [0.59 , 1.31]
Subtotal (95% CI)		**213**		**214**	**100.0%**	**0.90 [0.61 , 1.30]**
Total events:	41		46			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
4.13.2 After dose 2						
VAC Bhandari 2009-IND (2)	41	176	27	180	100.0%	1.55 [1.00 , 2.41]
Subtotal (95% CI)		**176**		**180**	**100.0%**	**1.55 [1.00 , 2.41]**
Total events:	41		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
4.13.3 After dose 3						
VAC Bhandari 2009-IND (2)	40	177	10	181	100.0%	4.09 [2.11 , 7.92]
Subtotal (95% CI)		**177**		**181**	**100.0%**	**4.09 [2.11 , 7.92]**
Total events:	40		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.18 (P < 0.0001)						



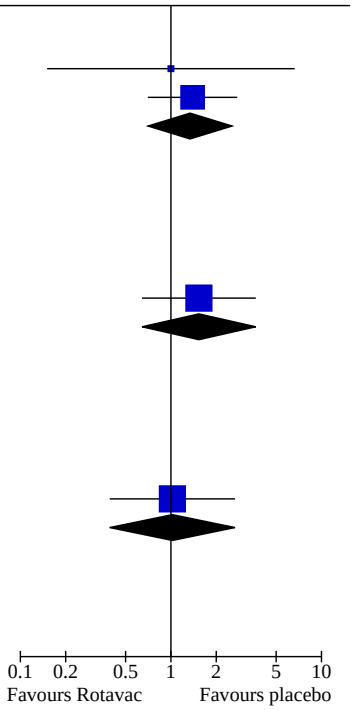
Footnotes

(1) intervention: 1 dose only

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

Analysis 4.14. Comparison 4: Rotavac versus placebo, Outcome 14: Reactogenicity: vomiting

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.14.1 After dose 1						
VAC Bhandari 2006-IND (1)	2	30	2	30	11.5%	1.00 [0.15 , 6.64]
VAC Bhandari 2009-IND (2)	18	183	13	184	88.5%	1.39 [0.70 , 2.76]
Subtotal (95% CI)		**213**		**214**	**100.0%**	**1.34 [0.70 , 2.55]**
Total events:	20		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
4.14.2 After dose 2						
VAC Bhandari 2009-IND (2)	12	176	8	180	100.0%	1.53 [0.64 , 3.66]
Subtotal (95% CI)		**176**		**180**	**100.0%**	**1.53 [0.64 , 3.66]**
Total events:	12		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
4.14.3 After dose 3						
VAC Bhandari 2009-IND (2)	8	177	8	181	100.0%	1.02 [0.39 , 2.66]
Subtotal (95% CI)		**177**		**181**	**100.0%**	**1.02 [0.39 , 2.66]**
Total events:	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						



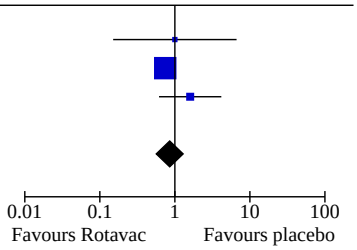
Footnotes

(1) intervention: 1 dose only

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

Analysis 4.15. Comparison 4: Rotavac versus placebo, Outcome 15: Dropouts before the end of the trial

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VAC Bhandari 2006-IND (1)	2	30	2	30	4.6%	1.00 [0.15 , 6.64]
VAC Bhandari 2014-IND	113	4532	76	2267	79.3%	0.74 [0.56 , 0.99]
VAC Chandola 2017-IND	24	1017	5	339	16.2%	1.60 [0.62 , 4.16]
Total (95% CI)		**5579**		**2636**	**100.0%**	**0.85 [0.57 , 1.29]**
Total events:	139		83			
Heterogeneity: Tau² = 0.03; Chi² = 2.33, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Not applicable						

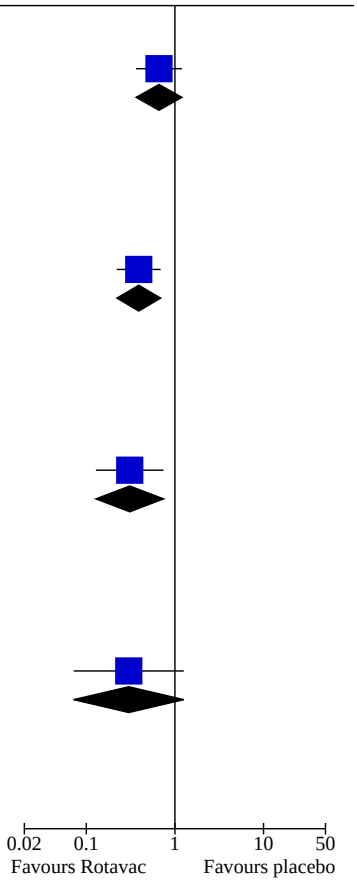


Footnotes

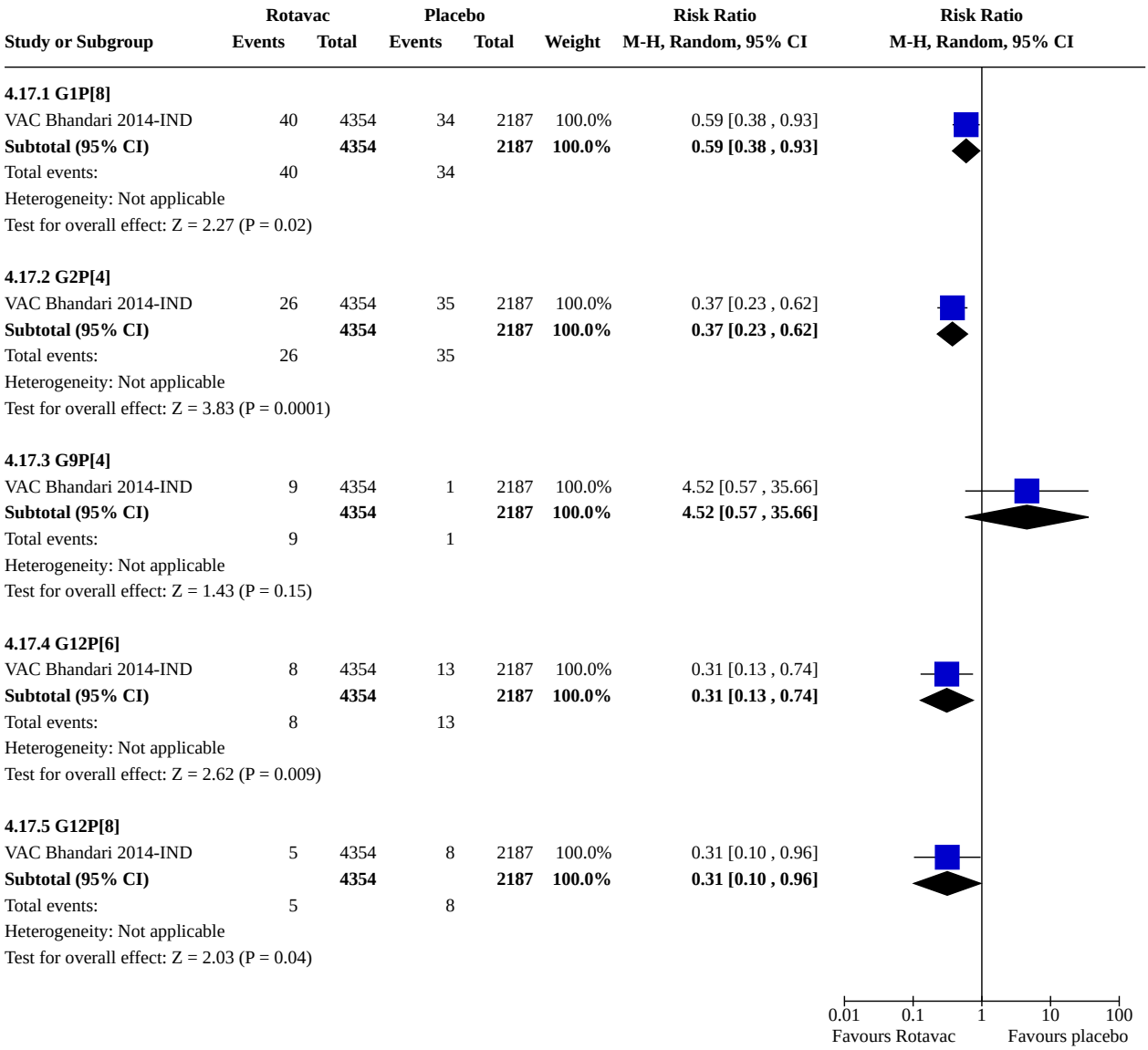
(1) intervention: 1 dose only

Analysis 4.16. Comparison 4: Rotavac versus placebo, Outcome 16: Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 1 year follow-up)

Study or Subgroup	Rotavac Events	Rotavac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.16.1 G1P[8]						
VAC Bhandari 2014-IND	25	4354	19	2187	100.0%	0.66 [0.36 , 1.20]
Subtotal (95% CI)		**4354**		**2187**	**100.0%**	**0.66 [0.36 , 1.20]**
Total events:	25		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
4.16.2 G2P[4]						
VAC Bhandari 2014-IND	21	4354	27	2187	100.0%	0.39 [0.22 , 0.69]
Subtotal (95% CI)		**4354**		**2187**	**100.0%**	**0.39 [0.22 , 0.69]**
Total events:	21		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.24 (P = 0.001)						
4.16.3 G12P[6]						
VAC Bhandari 2014-IND	8	4354	13	2187	100.0%	0.31 [0.13 , 0.74]
Subtotal (95% CI)		**4354**		**2187**	**100.0%**	**0.31 [0.13 , 0.74]**
Total events:	8		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.62 (P = 0.009)						
4.16.4 G12P[8]						
VAC Bhandari 2014-IND	3	4354	5	2187	100.0%	0.30 [0.07 , 1.26]
Subtotal (95% CI)		**4354**		**2187**	**100.0%**	**0.30 [0.07 , 1.26]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						



Analysis 4.17. Comparison 4: Rotavac versus placebo, Outcome 17: Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 2 years follow-up)



ADDITIONAL TABLES

Table 1. Prespecified changes for review update

Protocol section	Appraisal points	Address here
Background and research question	• Review and update background section, including supporting references to take account of any changes that may have occurred. This should include updating any new information and current policy debates on the topic.	Authors plan to update the Background section with any new relevant background information and references, but this will not have changed much since October 2019.
Inclusion criteria	• Review current PICO(s) and amend in light of new knowledge. • Identify any changes in usual care standards.	Authors plan to amend the types of outcome measures list:

Table 1. Prespecified changes for review update *(Continued)*

	• Check for standardized core outcome sets, such as those developed in collaboration with the core outcome measures in effectiveness trials (COMET) initiative (www.comet-initiative.org) or by guideline groups since the original review. • Check for any relevant patient reported outcomes to include subsequent to the original review. • Consider any new studies with less risk of bias that might warrant a stricter study design inclusion criteria (where the older version, when there was a dearth of evidence, included observational or quasi-randomized comparisons).	1) remove immunogenicity outcomes because there is plenty of high-certainty efficacy data, also for the new vaccines, and therefore no need to include immunogenicity outcomes for the objective of this review. 2) include 2nd year of life as a time point for primary efficacy outcomes (in addition to first year of life and up to two years).
Methods	• Appraise and update the methods pending relevant methodological advancements or developments. For example, if there are new tools for assessing the risk of bias of individual studies or appraising the quality of a body of evidence (e.g. GRADE). • Update or include a summary of findings table, which is recommended for all systematic reviews, because it improves the clarity, understanding, and interpretation of the findings of a systematic review, and rapidly reduces the amount of time readers require to find key information. • Any new subanalysis needed. • Any substantive change in the review structure.	1) Authors plan to update the country mortality stratification using the 2019 UNICEF report on levels and trends in child mortality https://reliefweb.int/sites/reliefweb.int/files/resources/UN-IGME-Child-Mortality-Report-2019.pdf. Data and summary of findings tables will be stratified based on country under-5 mortality: low-mortality countries are those in the lowest quartile of under-5 child mortality rates, medium-mortality countries are those in the second quartile, and high-mortality countries are those in the highest two quartiles. 2) Authors plan to carry out subgroup analyses for virus P-types (in addition to G-types that have been assessed in the current review). 3) Authors plan to use vaccine brand names (Rotarix, Rotasiil, RotaTeq, Rotavac with abbreviations rix, siil, teq, vac) since the previous way of naming the vaccines, based on number of strains, is no longer possible because the new vaccines have the same number of strains (one or five) as the old.

Submitted by the author team, and approved by the CIDG Editors 23 November 2020.

Table 2. Post hoc subgroup analysis: Intussusception combining all vaccines

Setting	Illustrative comparable risks* (95% CI)		Number of participants (studies)	RR (95% CI)
	Assumed risk Placebo	Corresponding risk Rotavirus vaccine		
Low-mortality countries	6 per 10,000	5 per 10,000 (3 to 9)	94,698 (19 RCTs)	0.87 (0.50 to 1.54)
	1 fewer per 10,000 (from 3 fewer to 3 more)			
Medium-mortality countries	6 per 10,000	5 per 10,000 (3 to 8)	79,622 (8 RCTs)	0.77 (0.43 to 1.40)
	1 fewer per 10,000 (from 3 fewer to 2 more)			

Table 2. Post hoc subgroup analysis: Intussusception combining all vaccines *(Continued)*

High-mortality countries	7 per 10,000	7 per 10,000 (3 to 15)	38,316 (16 RCTs)	1.04 (0.49 to 2.25)
	0 fewer per 10,000 (from 3 fewer to 8 more)			
All settings	6 per 10,000	5 per 10,000 (4 to 7)	212,636 (43 RCTs)	0.87 (0.61 to 1.25)
	1 fewer per 10,000 (from 2 fewer to 1 more)			

*The basis for the **assumed risk** is the control group risk across studies included in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT**: randomized controlled trial; **RR:** risk ratio

APPENDICES

Appendix 1. Trial type (efficacy or safety) and length of follow-up

Trial	Type: efficacy or safety	Follow-up time
RIX Anh 2011-PHL	Safety	1 month after last dose
RIX Anh 2011-VNM	Safety	1 month after last dose
RIX Bernstein 1998-USA	Safety	1 month
RIX Bernstein 1999-USA	Efficacy/safety	2 years
RIX Colgate 2016-BGD	Efficacy	1 year
RIX Dennehy 2005-NA	Safety	10 to 12 months
RIX GSK[021] 2007-PAN	Safety	1 month after dose 3
RIX GSK[033] 2007-LA	Safety	1 month
RIX GSK[041] 2007-KOR	Safety	2 months
RIX GSK[101555] 2008-PHL	Safety	1 month
RIX Kawamura 2011-JPN	Efficacy/safety	Up to the age of 2 years
RIX Kerdpanich 2010-THA	Safety	2 months after last dose
RIX Kim 2012-KOR	Safety	1 month after last dose
RIX Li 2013a-CHN	Safety	1 month
RIX Li 2013b-CHN	Safety	1 month

(Continued)

RIX Li 2014-CHN	Efficacy/safety	2 years
RIX Madhi 2010-AF	Efficacy/safety	2 years
RIX Narang 2009-IND	Safety	1 month
RIX NCT00158756-RUS	Safety	1 year
RIX Omenaca 2012-EU	Safety	At least 1 month after dose 2
RIX Phua 2005-SGP	Efficacy/safety	Until infant aged 18 months (i.e. 13 to 15 months)
RIX Phua 2009-AS	Efficacy/safety	3 years
RIX Rivera 2011-DOM	Safety	17 weeks after each dose
RIX Ruiz-Palac 06-LA/EU	Efficacy/safety	9 to 10 months
RIX Salinas 2005-LA	Efficacy/safety	Up to 2 years
RIX Steele 2008-ZAF	Safety	Up to 6 months
RIX Steele 2010a-ZAF	Safety	31 days after each dose, 42 days after the last dose
RIX Steele 2010b-ZAF	Safety	Up to 6 months
RIX Tregnaghi 2011-LA	Efficacy/safety	Up to age 1 year
RIX Vesikari 2004a-FIN	Safety	8 to 30 days after each dose
RIX Vesikari 2004b-FIN	Efficacy/safety	1 and 2 years (both reported)
RIX Vesikari 2007a-EU	Efficacy/safety	1 and 2 years (plus 3 years in Finland)
RIX Vesikari 2011-FIN	Safety	2 months
RIX Ward 2006-USA	Safety	7 days after each vaccination; 3 to 5 weeks after dose 2
RIX Zaman 2009-BGD	Safety	31 days
RIX Zaman 2017-BGD	Effectiveness	2 years
TEQ Armah 2010-AF	Efficacy/safety	Up to 43 days for safety outcomes, up to 21 months for efficacy outcomes
TEQ Block 2007-EU/USA	Efficacy/safety	42 days for safety/immunogenicity; 1 year for efficacy
TEQ Ciarlet 2009-EU	Safety	42 days
TEQ Clark 2003-USA	Efficacy/safety	1 year
TEQ Clark 2004-USA	Efficacy/safety	1 year

(Continued)

TEQ Dhingra 2014-IND	Safety	1 month
TEQ Iwata 2013-JPN	Efficacy/safety	25 months
TEQ Kim 2008-KOR	Safety	42 days
TEQ Lawrence 2012-CHN	Safety	2 weeks after last dose
TEQ Levin 2017-AF	Safety	1 month
TEQ Merck[009] 2005-USA	Safety	42 days
TEQ Mo 2017-CHN	Efficacy/safety	2 years
TEQ Vesikari 2006a-FIN	Efficacy/safety	1 to 3 years
TEQ Vesikari 2006b-INT	Efficacy/safety	43 days for safety; 2 years for efficacy
TEQ Zaman 2010-AS	Efficacy/safety	Up to 43 days for safety outcomes, up to 2 years for efficacy outcomes
SIIL Isanaka 2017-NER	Efficacy/safety	2 years
SIIL Kulkarni 2017-IND	Efficacy/safety	2 years
SIIL Zade 2014-INDa	Safety	1 month
SIIL Zade 2014-INDb	Safety	1 month
SIIL Zade 2014-INDc	Safety	1 month
VAC Bhandari 2006-IND	Safety	1 month
VAC Bhandari 2009-IND	Safety	12 weeks
VAC Bhandari 2014-IND	Efficacy/safety	Up to 2 years of age
VAC Chandola 2017-IND	Safety	1 year

Appendix 2. Efficacy outcome measures by trial

Trial	Rotavirus diarrhoea (any severity)			All-cause diarrhoea		ED visit	Hospitalization (all-cause)	All-cause death	Dropouts
	All	Severe	Hospital	All	Severe				
RIX Anh 2011-PHL	X	-	-	X	-	-	-	X	X
RIX Anh 2011-VNM	X	-	-	X	-	-	-	X	X
RIX Bernstein 1998-USA	-	-	-	-	-	-	-	-	-
RIX Bernstein 1999-USA	X	X	X	X[a]	-	X[a]	-	X	-
RIX Colgate 2016-BGD	X	X	-	X	X	-	-	X	X
RIX Dennehy 2005-NA	-	-	-	-	-	-	-	-	-
RIX GSK[021] 2007-PAN	-	-	-	-	-	-	-	X	X
RIX GSK[033] 2007-LA	-	-	-	-	-	-	-	X	X
RIX GSK[041] 2007-KOR	X	-	-	-	-	-	-	X	X
RIX GSK[101555] 2008-PHL	X	-	-	-	-	-	-	X	X
RIX Kawamura 2011-JPN	-	X	X	-	-	-	-	X	X
RIX Kerdpanich 2010-THA	X	-	-	X	-	-	-	X	X
RIX Kim 2012-KOR	X	-	-	X	-	-	-	X	X
RIX Li 2013a-CHN	-	-	-	-	-	-	-	X	X
RIX Li 2013b-CHN	-	-	-	-	-	-	-	-	-
RIX Li 2014-CHN	X	X	X	X	X	-	-	X	X
RIX Madhi 2010-AF	X	X	X	-	X	-	-	X	X
RIX Narang 2009-IND	X	-	-	-	-	-	-	X	X

(Continued)

RIX NCT00158756-RUS	-	-	-	-	-	-	-	X	X
RIX Omenaca 2012-EU	X	-	-	X	-	-	-	-	X
RIX Phua 2009-AS	X[a]	X	X	X[a]	X		X[a]	X	
RIX Phua 2005-SGP	X	X	X	X	X	X	X	X	X
RIX Rivera 2011-DOM	X	-	-	X	-	-	-	-	X
RIX Ruiz-Palac 06-LA/EU	X[a]	X	X	X[a]	X	-	X[a]	X	X[a]
RIX Salinas 2005-LA	X	X	X	X	X[a]	-	X[a]	X	
RIX Steele 2008-ZAF	-	-	-	-	-	-	-	X	X
RIX Steele 2010a-ZAF	X	-	-	X	-	-	-	X	X
RIX Steele 2010b-ZAF	X	X	-	-	-	-	-	X	X
RIX Tregnaghi 2011-LA	-	X	-	-	X[a]	-	-	X	X
RIX Vesikari 2004a-FIN	-	-	-	-	-	-	-	X[a]	X
RIX Vesikari 2004b-FIN	X	X	X	X	-	-	-	X	X
RIX Vesikari 2007a-EU	X	X	X	X[a]	X	X[a]	X[a]	-	-
RIX Vesikari 2011-FIN	X	-	-	X	-	-	-	X	X
RIX Ward 2006-USA	-	-	-	-	-	-	-	-	-
RIX Zaman 2009-BGD	X	-	-	-	-	-	-	X	
RIX Zaman 2017-BGD	-	X	-	-	-	-	-	-	-
TEQ Armah 2010-AF	X	X	-	X	X	-	-	X	X
TEQ Block 2007-EU/USA	X	X	-	-	-	-	-	X	X
TEQ Ciarlet 2009-EU	-	-	-	-	-	-	-	X	-

(Continued)

TEQ Clark 2003-USA	X	X[a]	-	-	-	-	-	-	X
TEQ Clark 2004-USA	X	X	-	-	-	-	-	-	X
TEQ Dhingra 2014-IND	-	-	-	-	-	-	-	-	X
TEQ Iwata 2013-JPN	X	X	-	-	-	-	-	X	X
TEQ Kim 2008-KOR	-	-	-	-	-	-	-	-	-
TEQ Lawrence 2012-CHN	-	-	-	-	-	-	-	X	X
TEQ Levin 2017-AF	-	-	-	-	-	-	-	X	X
TEQ Merck[009] 2005-USA	-	-	-	-	-	-	-	X	X
TEQ Mo 2017-CHN	-	-	-	-	-	-	-	X	X
TEQ Vesikari 2006a-FIN	X	X	-	-	-	-	-	X	X
TEQ Vesikari 2006b-INT	X	X	X	-	-	X[a]	X[a]	X	X
TEQ Zaman 2010-AS	X	X	-	-	X	-	-	X	X
SIIL Isanaka 2017-NER	X	X	-	X	X	-	-	X	X
SIIL Kulkarni 2017-IND	X	X	X	-	X	-	-	X	X
SIIL Zade 2014-INDa	-	-	-	-	-	-	-	-	-
SIIL Zade 2014-INDb	-	-	-	-	-	-	-	-	-
SIIL Zade 2014-INDc	-	-	-	-	-	-	-	-	-
VAC Bhandari 2006-IND	-	-	-	-	-	-	-	-	X
VAC Bhandari 2009-IND	-	-	-	-	-	-	-	-	-
VAC Bhandari 2014-IND	X	X	X	-	X	-	-	X	X
VAC Chandola 2017-IND	-	-	-	-	-	-	-	X	X

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

Appendix 3. Safety outcome measures by trial

Trial	Safety		
	Serious AE	Reactogenicity	AE to discontinuation
RIX Anh 2011-PHL	X	X	X
RIX Anh 2011-VNM	X	X	X
RIX Bernstein 1998-USA	X	X	X
RIX Bernstein 1999-USA	-	X	-
RIX Colgate 2016-BGD	-	-	-
RIX Dennehy 2005-NA	X	X	X
RIX GSK[021] 2007-PAN	X	X	X
RIX GSK[033] 2007-LA	X	X	X
RIX GSK[041] 2007-KOR	X	X	X
RIX GSK[101555] 2008-PHL	X	X	X
RIX Kawamura 2011-JPN	X	X	X
RIX Kerdpanich 2010-THA	X	X	X
RIX Kim 2012-KOR	X	X	X
RIX Li 2013a-CHN	X	X	X
RIX Li 2013b-CHN	-	-	-
RIX Li 2014-CHN	X	X	X
RIX Madhi 2010-AF	X	-	-
RIX Narang 2009-IND	X	X	X
RIX NCT00158756-RUS	X	-	X
RIX Omenaca 2012-EU	X	X	-
RIX Phua 2005-SGP	X	X	X[a]
RIX Phua 2009-AS	X	-	X
RIX Rivera 2011-DOM	X	X	-
RIX Ruiz-Palac 06-LA/EU	X	X	X

(Continued)

RIX Salinas 2005-LA	X	X	-
RIX Steele 2008-ZAF	X	X	X
RIX Steele 2010a-ZAF	X	X[a]	-
RIX Steele 2010b-ZAF	X	X	X
RIX Tregnaghi 2011-LA	X	-	X
RIX Vesikari 2004a-FIN	X	X	X
RIX Vesikari 2004b-FIN	X	X	X
RIX Vesikari 2007a-EU	X	X	-
RIX Vesikari 2011-FIN	X	X	X
RIX Ward 2006-USA		X[a]	-
RIX Zaman 2009-BGD	X	X	-
RIX Zaman 2017-BGD	X	-	-
TEQ Armah 2010-AF	X	X[a]	X
TEQ Block 2007-EU/USA	X	X	X
TEQ Ciarlet 2009-EU	X	X	-
TEQ Clark 2003-USA	X	X	X
TEQ Clark 2004-USA	X[a]	X	X
TEQ Dhingra 2014-IND	X	X	X
TEQ Iwata 2013-JPN	X[a]	X	X
TEQ Kim 2008-KOR	X	X[a]	-
TEQ Lawrence 2012-CHN	X	X[a]	X
TEQ Levin 2017-AF	X	X	X
TEQ Merck[009] 2005-USA	X	X	X
TEQ Mo 2017-CHN	X	X	X
TEQ Vesikari 2006a-FIN	X	X	X
TEQ Vesikari 2006b-INT	X	X	X[a]
TEQ Zaman 2010-AS	X	X[a]	X
SIIL Isanaka 2017-NER	X	X	-

(Continued)

SIIL Kulkarni 2017-IND	X	X	X
SIIL Zade 2014-INDa	X	X[a]	-
SIIL Zade 2014-INDb	X	X	-
SIIL Zade 2014-INDc	X	X	-
VAC Bhandari 2006-IND	X	X	-
VAC Bhandari 2009-IND	X	X	-
VAC Bhandari 2014-IND	X	-	-
VAC Chandola 2017-IND	X	-	-

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

Appendix 4. Trial location

Trial	Year	Location	Sites	Country mortality rate	Region
RIX Anh 2011-PHL	2007	Philippines	1	High-mortality	Asia
RIX Anh 2011-VNM	2007	Vietnam	11	High-mortality	Asia
RIX Bernstein 1998-USA	1998	USA	1	Low-mortality	North America
RIX Bernstein 1999-USA	1999	USA	2	Low-mortality	North America
RIX Colgate 2016-BGD	2014	Bangladesh	1	High-mortality	Asia
RIX Dennehy 2005-NA	2005	USA and Canada	41	Low-mortality	North America
RIX GSK[021] 2007-PAN	2007	Panama	1	Medium-mortality	Latin America
RIX GSK[033] 2007-LA	2007	Colombia, Mexico, and Peru	(2 in Colombia, 1 in Mexico, and 4 in Peru)	Medium-mortality	Latin America
RIX GSK[041] 2007-KOR	2007	South Korea	6	Low-mortality	Asia
RIX GSK[101555] 2008-PHL	2008	Philippines	1	High-mortality	Asia
RIX Kawamura 2011-JPN	2009	Japan	18	Low-mortality	Asia
RIX Kerdpanich 2010-THA	2005	Thailand	2	Medium-mortality	Asia
RIX Kim 2012-KOR	2010	Republic of Korea	19	Low-mortality	Asia

(Continued)

RIX Li 2013a-CHN	2010	China	1	Medium-mortality	Asia
RIX Li 2013b-CHN	2010	China	1	Medium-mortality	Asia
RIX Li 2014-CHN	2012	China	4	Medium-mortality	Asia
RIX Madhi 2010-AF	2010	South Africa and Malawi	2	High-mortality	Africa
RIX Narang 2009-IND	2009	India	4	High-mortality	Asia
RIX NCT00158756-RUS	2006	Russian Federation	9	Medium-mortality	Europe
RIX Omenaca 2012-EU	2008	France, Poland, Portugal, and Spain	Multiple sites in each country	Low-mortality	Europe
RIX Phua 2005-SGP	2005	Singapore	8	Low-mortality	Asia
RIX Phua 2009-AS	2009	Hong Kong, Singapore, and Taiwan	3	Low-mortality	Asia
RIX Rivera 2011-DOM	2008	Dominican Republic	1	High-mortality	Latin America
RIX Ruiz-Palac 06-LA/EU	2006	Argentina, Brazil, Chile, Colombia, Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	Multiple	Medium-mortality[a]	Latin America/Europe
RIX Salinas 2005-LA	2005	Brazil, Mexico, and Venezuela	3	Medium-mortality[b]	Latin America
RIX Steele 2008-ZAF	2007	South Africa	1	High-mortality	Africa
RIX Steele 2010a-ZAF	2008	South Africa	5	High-mortality	Africa
RIX Steele 2010b-ZAF	2007	South Africa	7	High-mortality	Africa
RIX Tregnaghi 2011-LA	2008	Argentina, Brazil, Colombia, Dominican Republic, Honduras, and Panama	Multiple sites in each country	Medium-mortality[c]	Latin America
RIX Vesikari 2004a-FIN	2004	Finland	2	Low-mortality	Europe
RIX Vesikari 2004b-FIN	2004	Finland	6	Low-mortality	Europe
RIX Vesikari 2007a-EU	2007	Czech Republic, Finland, France, Germany, Italy, and Spain	98	Low-mortality	Europe
RIX Vesikari 2011-FIN	2005	Finland	5	Low-mortality	Europe
RIX Ward 2006-USA	2006	USA	2	Low-mortality	North America

(Continued)

RIX Zaman 2009-BGD	2005	Bangladesh	1	High-mortality	Asia
RIX Zaman 2017-BGD	2011	Bangladesh	142	High-mortality	Asia
TEQ Armah 2010-AF	2009	Ghana, Kenya, and Mali	3	High-mortality	Africa
TEQ Block 2007-EU/USA	2007	Finland and USA	30	Low-mortality	Europe and North America
TEQ Ciarlet 2009-EU	2008	Austria, Belgium, and Germany	26	Low-mortality	Europe
TEQ Clark 2003-USA	2003	USA	19	Low-mortality	North America
TEQ Clark 2004-USA	2004	USA	10	Low-mortality	North America
TEQ Dhingra 2014-IND	2012	India	2	High-mortality	Asia
TEQ Iwata 2013-JPN	2009	Japan	32	Low-mortality	Asia
TEQ Kim 2008-KOR	2008	South Korea	8	Low-mortality	Asia
TEQ Lawrence 2012-CHN	2010	China	Not reported	Medium-mortality	Asia
TEQ Merck[009] 2005-USA	2005	USA	10	Low-mortality	North America
TEQ Mo 2017-CHN	2015	China	5	Medium-mortality	Asia
TEQ Vesikari 2006a-FIN	2006	Finland	4	Low-mortality	Europe
TEQ Vesikari 2006b-INT	2006	Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and USA	356	Low-mortality[d]	Asia, Caribbean, Europe, Latin America, North America
TEQ Zaman 2010-AS	2009	Bangladesh and Vietnam	Multiple	High-mortality	Asia
SIIL Isanaka 2017-NER	2014-15	Niger	1	High-mortality	Africa
SIIL Kulkarni 2017-IND	2014-17	India	6	High-mortality	Asia
SIIL Zade 2014-INDa	2009	India	1	High-mortality	Asia
SIIL Zade 2014-INDb	Not reported	India	1	High-mortality	Asia
SIIL Zade 2014-INDc	2011	India	2	High-mortality	Asia
VAC Bhandari 2006-IND	2005	India	1	High-mortality	Asia
VAC Bhandari 2009-IND	2006-8	India	1	High-mortality	Asia
VAC Bhandari 2014-IND	2011-13	India	3	High-mortality	Asia

(Continued)

VAC Chandola 2017-IND	2014-15	India	1	High-mortality	Asia

[a]RIX Ruiz-Palac 06-LA/EU was conducted mainly in medium-mortality Argentina, Brazil, Chile, Colombia, Mexico, Panama, and Peru, but also in low-mortality Finland and high-mortality Dominican Republic, Honduras, Nicaragua, and Venezuela.
[b]RIX Salinas 2005-LA was conducted mainly in medium-mortality Brazil and Mexico, but also in high-mortality Venezuela.
[c]RIX Tregnaghi 2011-LA was conducted mainly in medium-mortality Argentina, Brazil, Colombia, and Panama, but also in high-mortality Dominican Republic and Honduras.
[d]TEQ Vesikari 2006b-INT was conducted mainly in low-mortality Belgium, Finland, Germany, Italy, Puerto Rico, Sweden, Taiwan, and USA, but also in medium-mortality Costa Rica, Jamaica, Mexico and high-mortality Guatemala.

Appendix 5. Vaccine schedules

Trial	Number of doses	Time between doses (weeks)	Number of arms: vaccine/placebo	Infant vaccination status	Note
RIX Anh 2011-PHL	2	4 or 8	2/1	Commercially available diphtheria, tetanus, whole-cell pertussis (DTPw), hepatitis B (HBV) and oral poliovirus (OPV) vaccines were administered concomitantly with the study vaccine/placebo as part of the routine Expanded Programme of Immunization (EPI) in the Philippines	Compared different schedules: (1) vaccine dose at month 1 and 2, and placebo at day 0; and (2) vaccine dose at day 0 and month 2, and placebo at month 1
RIX Anh 2011-VNM	2	4 or 8	2/1	Commercially available diphtheria, tetanus, whole-cell pertussis (DTPw), hepatitis B (HBV) and oral poliovirus (OPV) vaccines were administered concomitantly with the study vaccine/placebo as part of the routine Expanded Programme of Immunization (EPI) in Vietnam	Compared different schedules: (1) vaccine dose at day 0 and month 1, and placebo at month 2; and (2) vaccine dose at day 0 and month 2, and placebo at month 1
RIX Bernstein 1998-USA	2	6 to 10	1/1	Rotavirus vaccine was separated from all other infant vaccines by at least 2 weeks	—
RIX Bernstein 1999-USA	2	6 to 10	1/1	Other vaccines separated from the trial vaccines by at least 2 weeks	—
RIX Colgate 2016-BGD	2	7	1/1 (no Rotarix)	Alongside Rotarix at 10 and 17 weeks of age the polio vaccine intervention was the administration of an injected, inactivated polio vaccine (IPV) dose replacing the 4th dose of tOPV at 39 weeks of age. Study children also received all standard EPI vaccines (BCG at birth; pentavalent vaccine (DPT, HepB, Hib) at 6, 10, and 14 weeks; bivalent measles-rubella at 40	Rotarix plus polio vaccine (IPV), observational control group only

(Continued)

				weeks; and monovalent measles at 65 weeks)	
RIX Dennehy 2005-NA	2	7	2/1	Vaccine or placebo given concomitantly with diphtheria-tetanus-acellular pertussis, inactivated poliovirus, *H influenzae* type b, and *S pneumoniae* conjugate vaccines for participants in USA or with a diphtheria-tetanus-acellular pertussis/inactivated poliovirus/*H influenza* type b combination vaccine for participants in Canada "Routine hepatitis B vaccinations were administered according to local practice."	2 different PFUs compared
RIX GSK[021] 2007-PAN	3	8	2/2	Use of other vaccines not mentioned	Licensed formulation versus modified formulation
RIX GSK[033] 2007-LA	2	8	3/1	Use of other vaccines not mentioned	3 'Lots' of Rotarix vaccine compared
RIX GSK[041] 2007-KOR	2	8	1/1	*H influenzae* type b vaccine administered concomitantly along with the 2 doses of vaccine/placebo and at 2 months after dose 2; other routine childhood vaccines were to be given at least 14 days before trial vaccine/placebo	—
RIX GSK[101555] 2008-PHL	2	8	2/2	No mention of whether infants received other vaccines	Data from the lyophilized formulation, which is not yet approved or marketed, were not reported
RIX Kawamura 2011-JPN	2	4	1/1	Combined diphtheria and tetanus toxoids and acellular pertussis (DTPa) and hepatitis B (HBV) vaccines were allowed to be co-administered along with Rotarix vaccine/placebo	—
RIX Kerdpanich 2010-THA	2	8	3/2	Diphtheria toxoid, tetanus toxoid, acellular pertussis, inactivated polio and *H influenzae* type b combination vaccine (*Infanrix*™-IPV/Hib) at 2 and 4 months of age and diphtheria toxoid, tetanus toxoid, acellular pertussis, hepatitis B, inactivated polio and *H influenzae* type b combination vaccine (*Infanrix hexa*^{TM}) at 6 months of age	Compared: regular vaccine reconstituted in buffer; vaccine reconstituted in water; vaccine stored above recommended temperature; placebo reconstituted in water; placebo

(Continued)

					reconstituted in buffer
RIX Kim 2012-KOR	2	4	1/1	Routine childhood vaccines as recommended by the local vaccination schedule were allowed to be administered concomitantly with RIX4414/placebo. These vaccines included the combined diphtheria-tetanus-acellular pertussis vaccine, *Hemophilus influenzae* type b vaccine, inactivated poliovirus vaccine and pneumococcal vaccine. The infants had received the BCG vaccine and 2 doses of hepatitis B vaccine prior to study enrolment.	—
RIX Li 2013a-CHN	1	-	1/1	Children were allowed to receive routine childhood vaccinations according to local immunization practice during the study period, with a minimum interval of at least 7 days between the administration of routine vaccines and the study vaccine or placebo.	Child arm (2-6 years of age) of the same study as RIX Li 2013b-CHN
RIX Li 2013b-CHN	1	-	1/1	Infants were allowed to receive routine childhood vaccinations according to local immunization practice during the study period, with a minimum interval of at least 7 days between the administration of routine vaccines and the study vaccine or placebo.	Infant arm (6-16 weeks of age) of the same study as RIX Li 2013a-CHN
RIX Li 2014-CHN	2	4	2/2	As part of the routine childhood vaccination according to the EPI recommendations in China, participants also received 3 doses of Infanrix™ vaccine and 3 doses of the oral poliovirus vaccine. The Infanrix™ and the OPV vaccines were administered independently of (sub-cohort 1) or concomitantly with (sub-cohort 2) the Rotarix™ vaccine. When administered concomitantly, participants received the 3 doses of Infanrix™ vaccine at months 1, 2 and 3, and the 3 doses of the OPV vaccine at day 0, month 1 and month 2.	—
RIX Madhi 2010-AF	2 or 3	5 to 10	2/1	All participants received routine infant vaccinations according to EPI recommendations.	—
RIX Narang 2009-IND	2	8	1/1	Routine vaccinations (diphtheria-tetanus-whole cell pertussis-hepatitis b, *H influenzae* type b, and oral poliovirus vaccine) were administered at 6, 10, and 14 weeks of age (given with a 2-week separation from the first and subsequent dose of the Rotarix vaccine or placebo).	—

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RIX NCT00158756-RUS	3	6	5	GlaxoSmithKline (GSK) Biologicals' Tritanrix™HepB and GSK Biologicals Kft's DTPw-HBV vaccines as compared to concomitant administration of Commonwealth Serum Laboratory's (CSL's) DTPw (Triple Antigen™) and GSK Biologicals' HBV (Engerix™B), when co-administered With GSK Biologicals' Oral Live Attenuated Human Rotavirus (HRV) vaccine, to healthy infants at 3, 4½ and 6 months of age, after a birth dose of hepatitis B vaccine.	HepB and DTPw-HBV vaccines in combination with other vaccines/placebo were compared in the study arms.
RIX Omenaca 2012-EU	2	4 or 8	1/1	All participants received routine infant vaccinations in accordance with the local National Plan of Immunization schedule in each of the respective participating countries.	—
RIX Phua 2005-SGP	2	4	3/1	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, poliovirus, and *H influenzae* type b co-administered with interventions	3 different PFUs compared
RIX Phua 2009-AS	2	6 to 10	1/1	Infants received other routine paediatric immunizations (combined diphtheria toxoid-tetanus toxoid-acellular pertussis (DTPa) – inactivated poliovirus [IPV] and *H influenzae* type B (Hib) vaccine and hepatitis B vaccine (HBV)) during the study period according to local schedules. Almost all infants received BCG dose at birth. If oral polio vaccine (OPV) was given as part of the routine schedule in the participating countries, a time interval of 2 weeks was observed between the OPV doses and RIX4414 vaccine/placebo doses.	—
RIX Rivera 2011-DOM	2	7	1/1	All infants received 3 doses of combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus and *H influenzae* vaccine.	1 complimentary dose of Rotarix was administered to all infants enrolled in this study (both study groups) who were aged < 6 months at visit 3 (Week 13) as a benefit to the placebo group for participation in the study.
RIX Ruiz-Palac 06-LA/EU	2	4 or 8	1/1	Routine immunizations according to local regulations; oral poliovirus vaccination at least 2 weeks before or after rotavirus vaccine	—

(Continued)

RIX Salinas 2005-LA	2	8	3/1	Oral polio vaccine given after 2 weeks, not together with Rotarix	3 different PFUs compared Main publication did not report that the trial included 2 subsets: 2 doses of human rotavirus or placebo subset: these participants received 2 oral doses of Rotarix 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 Rotarix or placebo subset: these participants received 3 oral doses of Rotarix vaccine or placebo, and routine vaccinations (DTPw-HBV + Hib vaccine) concomitantly with each dose of human rotavirus vaccine and placebo at a 0, 2, and 4 months schedule.
RIX Steele 2008-ZAF	2	4	3/1	Rotarix plus (1) oral polio vaccine (OPV) + diphtheria-tetanus-acellular pertussis/*H influenzae* type b (DTPa/HIB) vaccine; (2) OPV placebo + diphtheria-tetanus-acellular pertussis inactivated polio-*H influenzae* type b (DTPa-IPV/HIB) vaccine; or (3) OPV + DTPa/HIB vaccine	Compared different co-administration combinations (see previous column)
RIX Steele 2010a-ZAF	3	4	1/1	Rotarix vaccine was concomitantly administered with 3 doses of combined diphtheria, tetanus and whole-cell pertussis, hepatitis B, and *H influenzae* type b	For infants who developed clinical symptoms of HIV (WHO stages III or IV disease)

(Continued)

				vaccine (TritanrixHepBHib) and OPV (PolioSabin)	any time after enrolment, access to antiretroviral therapy (cotrimoxazole) according to the South African national guidelines was facilitated. Infants who needed treatment were referred to antiretroviral therapy centres by the investigators.
RIX Steele 2010b-ZAF	2 or 3	4	2/1	Infants received routine vaccinations according to the local EPI schedule in South Africa. BCG and OPV vaccinations were given at birth; all other routine vaccinations (including diphtheria-tetanus toxoids-whole cell pertussis, hepatitis B, *H influenzae* type b, and OPV) were administered concomitantly with the study vaccine.	Compared number of doses (2 or 3)
RIX Tregnaghi 2011-LA	2	4 or 8	1/1	All participants received routine infant vaccinations (hepatitis B vaccine), diphtheria-tetanus-acellular pertussis, poliovirus, and *H influenzae* type b) according to EPI recommendations in each country. First 2 doses of routine EPI vaccinations were co-administered with the Rotarix vaccine or placebo doses; the 3rd routine EPI vaccination was administered 1 to 2 months later according to the national plan of immunization in each country.	—
RIX Vesikari 2004a-FIN	2	8	3/1	Infant routine vaccinations were separated from the study vaccines by 2 weeks.	3 different PFUs compared
RIX Vesikari 2004b-FIN	2	8	1/1	Infant routine vaccinations (diphtheria tetanus toxoids-pertussis, *H influenzae* type b, and inactivated poliovirus vaccines) were separated from the study vaccines by at least 2 weeks.	—
RIX Vesikari 2007a-EU	2	4 or 8	1/1	Concomitant vaccines included 7 valent pneumococcal polysaccharide conjugate vaccine (Prevenar) and meningococcal group c conjugate vaccine (Meningitec); hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, polio virus, and *H influenzae* type b vaccines were co-administered.	—

(Continued)

RIX Vesikari 2011-FIN	2	4	2/2	Routine childhood vaccinations were allowed according to local practice, but at least 14 days apart from each dose of study vaccine.	Compared liquid and lyophilized vaccine formulations
RIX Ward 2006-USA	2	4	2/1	Not specified	2 different PFUs compared
RIX Zaman 2009-BGD	2	—	2/2	All children in the study received the standard EPI vaccines starting at 6 weeks of age. Oral polio vaccine (OPV) co-administered in trial: either concomitantly with Rotarix or 15 days before Rotarix	Compared Rotarix plus oral polio vaccine with Rotarix alone
RIX Zaman 2017-BGD	2	4	1/1 (no Rotarix vaccine)	HRV was scheduled to be given along with other standard infant vaccines including OPV at the DTP dose 1 and 2 immunization visits, recommended in Bangladesh to occur at 6 and 10 weeks of age.	Cluster-randomized trial
TEQ Armah 2010-AF	3	4	1/1	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age.	—
TEQ Block 2007-EU/USA	3	4 to 10	1/1	Use of oral poliovirus vaccine during the course of the study or within 42 days before first dose of vaccine/placebo was an exclusion criterion; administration of other vaccines permitted	—
TEQ Ciarlet 2009-EU	3	4 to 6	1/1	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, polio virus, and *H influenzae* type b co-administered	—
TEQ Clark 2003-USA	3	6 to 8	1/1	Children that had recently received oral polio vaccine were excluded from the study.	Breastfed; infants in the vaccine control group (group 1) received the reassortants as administered in previous studies within 30 mins of feeding Enfamil formula (30 mL) or Mylanta Double Strength (0.5 mL/kg). Infants in a corresponding placebo group (group 2) were pre-fed as in group 1.

(Continued)

TEQ Clark 2004-USA	3	6 to 8	1/1	Receipt of any other vaccines within 14 days was not allowed.	—
TEQ Dhingra 2014-IND	3	4	4/1	Infants in cohort 2 concomitantly received a combined DTPw-HB-Hib pentavalent vaccine and Trivalent Oral Polio Vaccine	BRV-TV at 3 different concentrations, compared to RotaTeq or placebo
TEQ Iwata 2013-JPN	3	4 to 10	1/1	No information about use of other vaccines	—
TEQ Kim 2008-KOR	3	4 to 10	1/1	Infants excluded if they had or were to receive oral poliovirus vaccine at any time during the study or in the 42 days before the first dose; concomitant administration of other licensed vaccines and breastfeeding was not restricted.	—
TEQ Lawrence 2012-CHN	3	4-10	1/1	Other live vaccines 14 days before or after study vaccine were not allowed.	—
TEQ Levin 2017-AF	3	4-10	1/1	Enrolment was closed in participating countries when Rotarix was added to national vaccine schedules.	—
TEQ Merck[009] 2005-USA	3	4 to 10	1/1	Infants were excluded if they had or were to receive oral poliovirus vaccine at any time during the study or in the 42 days before the first dose; concomitant administration of other licensed vaccines and breastfeeding was not reported.	—
TEQ Mo 2017-CHN	3	4	2/2	The routine China EPI vaccines (oral poliovirus vaccine and diphtheria, tetanus, and acellular pertussis vaccine) either staggered or concomitantly with RotaTeq or placebo	—
TEQ Vesikari 2006a-FIN	3	4 to 8	3/1	Licensed vaccines could be administered throughout the study, but were not given on the same day as study vaccine; inactivated poliovirus vaccine was exclusively used in Finland at the time of the study.	Compared different RotaTeq components: G1-4, P1A; G1-4; and P1A
TEQ Vesikari 2006b-INT	3	4 to 10	1/1	Administration of other licensed childhood vaccines and breastfeeding were not restricted; for a subset of participants in the USA (U.A. concomitant use cohort), Merck also provided the licensed paediatric vaccines that were administered concomitantly (same day) with RotaTeq or placebo, which included Comvax, Infanrix, Ipol, and Prevnar.	—
TEQ Zaman 2010-AS	3	4	1/1	All children in the study received the standard EPI vaccines (including oral po-	—

(Continued)

				liovirus vaccine) starting at 6 weeks of age.	
SIIL Isanaka 2017-NER	3	4	1/1	Vaccines that were routinely administered according to the guidelines of the EPI were concomitantly administered with the vaccine or placebo.	—
SIIL Kulkarni 2017-IND	3	4	1/1	The routine DTP-hepatitis B-Hib and oral polio vaccines were administered concomitantly.	—
SIIL Zade 2014-INDa	1	-	1/1	-	—
SIIL Zade 2014-INDb	3	4	1/1	-	—
SIIL Zade 2014-INDc	3	4	1/1	Other childhood vaccines such as DTP, OPV, hepatitis B vaccine, *Haemophilus influenzae* type b, or BCG with at least 7 days separation from the first and subsequent dose of the study vaccine	—
VAC Bhandari 2006-IND	1	-	1/1 (/1)	Infants were vaccinated with DPT, HepB and OPV separately from rotavirus vaccine.	Included an additional vaccine arm for a rotavirus vaccine candidate (I321) that was not included for analysis in this review
VAC Bhandari 2009-IND	3	4	2/2	Infants received 3 doses of DTP; OPV; and HepB at 6, 10, and 14 weeks of age; Rotavac was administered at 8, 12, and 16 weeks of age.	Randomized participants to high- (1×10^5 ffu) and low-dose (1×10^4 ffu) vaccine arms which were combined in this review
VAC Bhandari 2014-IND	3	4	1/1	Other childhood vaccines (DTPw, Hib, HepB, and OPV) given concurrently	—
VAC Chandola 2017-IND	3	4-8	3/1	Co-administered with EPI vaccines: OPV and combined DPT, HepB and Hib	Randomized participants to 3 vaccine production lots as well as to placebo; we combined the different production lot arms in our analyses.

BCG: Bacille Calmette Guérin

BRV-TV: bovine rotavirus tetravalent vaccine

CSL: Commonwealth Serum Laboratory
DTP(a/w): diphtheria, tetanus, pertussis (acellular/whole cell)
EPI: Extended Programme of Immunization
FFU: focus-forming unit
GSK: GlaxoSmithKline
H influenzae: Haemophilus influenzae
HBV: Hepatitis B vaccine
HepB: Hepatitis B vaccine
Hib: *Haemophilus influenzae b*
HIV: human immunodeficiency virus
HRV: human rotavirus vaccine (Rotarix)
IPV: inactivated polio vaccine
OPV: oral polio vaccine
PFU: plaque-forming unit.
RIX4414: Rotarix vaccine
tOPV: trivalent oral polio vaccine
WHO: World Health Organization

Appendix 6. Methods to collect adverse event data

Trial	Passive or active
RIX Anh 2011-PHL	Not reported
RIX Anh 2011-VNM	Not reported
RIX Bernstein 1998-USA	Passive
RIX Bernstein 1999-USA	Passive and active
RIX Colgate 2016-BGD	Passive
RIX Dennehy 2005-NA	Passive and active
RIX GSK[021] 2007-PAN	Not reported
RIX GSK[033] 2007-LA	Not reported
RIX GSK[041] 2007-KOR	Not reported
RIX GSK[101555] 2008-PHL	Not reported
RIX Kawamura 2011-JPN	Not reported
RIX Kerdpanich 2010-THA	Passive
RIX Kim 2012-KOR	Passive
RIX Li 2013b-CHN	Passive
RIX Li 2014-CHN	Not reported
RIX Madhi 2010-AF	Active
RIX Narang 2009-IND	Passive

(Continued)

RIX NCT00158756-RUS	Not reported
RIX Omenaca 2012-EU	Not reported
RIX Phua 2005-SGP	Passive
RIX Phua 2009-AS	Passive
RIX Rivera 2011-DOM	Passive
RIX Ruiz-Palac 06-LA/EU	Active
RIX Salinas 2005-LA	Passive
RIX Steele 2008-ZAF	Not reported
RIX Steele 2010a-ZAF	Active and passive
RIX Steele 2010b-ZAF	Not reported
RIX Tregnaghi 2011-LA	Not reported
RIX Vesikari 2004a-FIN	Passive
RIX Vesikari 2004b-FIN	Passive
RIX Vesikari 2007a-EU	Passive and active
RIX Vesikari 2011-FIN	Passive
RIX Ward 2006-USA	Not reported
RIX Zaman 2009-BGD	Passive and active
RIX Zaman 2017-BGD	Not reported
TEQ Armah 2010-AF	Active
TEQ Block 2007-EU/USA	Passive and active
TEQ Ciarlet 2009-EU	Passive and active
TEQ Clark 2003-USA	Passive and active
TEQ Clark 2004-USA	Passive and active
TEQ Dhingra 2014-IND	Passive and active
TEQ Iwata 2013-JPN	Passive
TEQ Kim 2008-KOR	Passive
TEQ Lawrence 2012-CHN	Not reported
TEQ Levin 2017-AF	Active

(Continued)

TEQ Merck[009] 2005-USA	Not reported
TEQ Mo 2017-CHN	Passive
TEQ Vesikari 2006a-FIN	Passive and active
TEQ Vesikari 2006b-INT	Active
TEQ Zaman 2010-AS	Active and passive
SIIL Isanaka 2017-NER	Active and passive
SIIL Kulkarni 2017-IND	Active and passive
SIIL Zade 2014-INDa	Not reported
SIIL Zade 2014-INDb	Not reported
SIIL Zade 2014-INDc	Not reported
VAC Bhandari 2006-IND	Passive and active
VAC Bhandari 2009-IND	Passive and active
VAC Bhandari 2014-IND	Passive and active
VAC Chandola 2017-IND	Active

Appendix 7. Deaths[a]: from published trials and from communication with trial authors

Vaccine	Trial	No. of deaths				Cause of death
		Vaccine	Placebo	Unclear	Total	
Rotarix	RIX Anh 2011-PHL	1	0	0	1	*Salmonella* gastroenteritis
	RIX Anh 2011-VNM	0	0	0	0	—
	RIX Bernstein 1998-USA	0	0	0	0	—
	RIX Bernstein 1999-USA	0	0	1 (1)	1	Pneumococcal sepsis
	RIX Colgate 2016-BGD	1	1	0	2	Reasons not reported
	RIX GSK[021] 2007-PAN	0	0	0	0	—

(Continued)

RIX Tregnaghi 2011-LA	10	2	0	12	Meningitis bacterial (1 vaccine, 1 placebo), pneumonia (3 vaccine), aortic valve stenosis (1 vaccine), bronchiolitis (1 vaccine), dengue fever (1 vaccine), endocarditis bacterial (1 vaccine), intussusception (1 vaccine), multi-organ failure (1 placebo), respiratory failure (1 vaccine), sepsis (2 vaccine)
RIX GSK[033] 2007-LA	3	0	0	3	Gastroenteritis (1 vaccine), bronchopneumonia (1 vaccine), aspiration (1 vaccine)
RIX GSK[041] 2007-KOR	0	0	0	2	Not reported
RIX GSK[101555] 2008-PHL	0	0	0	0	—
RIX Kawamura 2011-JPN	0	0	0	0	—
RIX Kerdpanich 2010-THA	0	0	0	0	—
RIX Kim 2012-KOR	0	0	0	0	—
RIX Li 2013a-CHN	0	0	0	0	—
RIX Li 2013b-CHN	0	0	0	0	—
RIX Li 2014-CHN	6	7	0	13	Vaccine (6): asphyxia, drowning, central nervous system infection, bronchopneumonia, cortical dysplasia, intracranial haemorrhage, asphyxia, meningitis, multi-organ failure, haemotophagic histiocytosis, acute lymphocytic leukaemia, multi-organ failure Placebo (7): diarrhoea, multi-organ failure, congenital heart disease, respiratory failure, brain contusion, subarachnoid haemorrhage, skull fracture, cerebral haematoma, and brain herniation
RIX Madhi 2010-AF	83	43	0	126	Reasons not stated
RIX Narang 2009-IND	0	0	0	0	—

(Continued)

	RIX NCT00158756-RUS	0	0	0	0	—
	RIX Phua 2005-SGP	3	0	0	3	Leukaemia (1 vaccine); accident-induced subarachnoid haemorrhage (1 vaccine); cardiorespiratory failure after acute viral pneumonitis (1 vaccine)
	RIX Phua 2009-AS	1	3	0	4	Aspiration and metabolic disorder, adenoviral pneumonia, interstitial pneumonia, and sudden infant death syndrome (not stated which group)
	RIX Rivera 2011-DOM	0	0	0	0	—
	RIX Ruiz-Palac 06-LA/EU	56	43	0	99	Diarrhoea (4 vaccine, 2 placebo); pneumonia (16 vaccine, 6 placebo); other causes not mentioned
	RIX Salinas 2005-LA	2	1	0	3	Generalized visceral congestion (1 placebo); sepsis (1 vaccine); automobile accident (1 vaccine)
	RIX Steele 2008-ZAF	3	5	0	8	Bronchopneumonia (1 placebo), pneumonia (2 vaccine, 2 placebo), hepatic steatosis (1 placebo), brain oedema (1 vaccine, 1 placebo)
	RIX Steele 2010a-ZAF	6	9	0	15	Bronchopneumonia, sepsis, and gastroenteritis were the most common causes
	RIX Steele 2010b-ZAF	3	0	0	3	Bronchopneumonia and gastroenteritis (3 vaccines)
	RIX Vesikari 2004b-FIN	0	0	0	0	—
	RIX Vesikari 2007a-EU	0	0	0	0	—
	RIX Vesikari 2011-FIN	0	0	0	0	—
	RIX Zaman 2009-BGD	1	0	0	1	—
RotaTeq	TEQ Armah 2010-AF	76	82	0	158	Gastroenteritis (20 vaccine, 16 placebo); 11 deaths occurred in identified HIV-infected participants in Kenya; sudden infant death syndrome (1 placebo); other causes not mentioned
	TEQ Block 2007-EU/USA	1	0	0	1	Sudden infant death syndrome (1 vaccine)

(Continued)

	TEQ Ciarlet 2009-EU	0	0	0	0	—
	TEQ Iwata 2013-JPN	0	0	0	0	—
	TEQ Lawrence 2012-CHN	0	0	0	0	—
	TEQ Levin 2017-AF	1	2	0	3	Pneumonia
	TEQ Merck[009] 2005-USA	0	0	0	0	—
	TEQ Mo 2017-CHN	0	1	0	1	Reasons not reported
	TEQ Vesikari 2006a-FIN	0	0	0	0	—
	TEQ Vesikari 2006b-INT	24	20	0	44	Sudden infant death syndrome (7 vaccine and 7 placebo), other causes not mentioned
	TEQ Zaman 2010-AS	3	4	0	7	Not all causes reported; most common causes were drowning and sepsis
Rotasiil	SIIL Isanaka 2017-NER	58	49	0	107	Infections and infestations (47 vaccine, 49 placebo); metabolism and nutritional disorders (4 vaccine, 4 placebo); general disorders and administration site conditions (5 vaccine, 1 placebo); gastrointestinal disorders (1 vaccine, 0 placebo); congenital, familial and genetic disorders (1 vaccine, 0 placebo); injury, poisoning and procedural complications (0 vaccine, 1 placebo)
	SIIL Kulkarni 2017-IND	16	16	0	38	Multi-organ failure (1 placebo); sudden death (1 placebo); sudden infant death syndrome (1 vaccine, 1 placebo); dengue fever (1 vaccine); encephalitis (1 placebo); encephalitis viral (1 placebo); meningitis tuberculous (1 placebo); septic shock (2 vaccine); accidental poisoning (1 placebo); drowning (1 placebo); foreign body aspiration (1 vaccine); acute leukaemia (1 vaccine); asphyxia (1 vaccine); aspiration (1 vaccine, 1 placebo); bronchiolitis (1 vaccine); bronchopneumonia (1 vaccine, 1 placebo); lobar pneumonia (1 vaccine); lower respiratory tract infection (1 placebo); pneumonia (1 vaccine, 1 placebo); pneumonitis (1 vaccine); death (no further cause reported) (3 vaccine, 4 placebo)

(Continued)

	SIIL Zade 2014-INDa	—	—	—	—	—
	SIIL Zade 2014-INDb	—	—	—	—	—
	SIIL Zade 2014-INDc	—	—	—	—	—
Rotavac	VAC Bhandari 2014-IND	30	18	0	48	The most common causes of death were infection and infestations followed by general disorders and administration site conditions. Days after vaccination not reported. None were considered to be vaccine-related.
	VAC Chandola 2017-IND	5	0	0	5	Cause of death: sepsis and aspiration (79-141 days after Rotavac vaccination), unexplained sudden death (3 days after Rotavac vaccination). None were considered to be vaccine-related.

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

Appendix 8. Other licensed rotavirus vaccines in use

Vaccine	Vaccination schedule	Vaccine antigens	Manufacturer	License information
Lanzhou lamb rotavirus (LLR)	1 dose annually for children 2 months to 3 years and one booster dose at 3 to 5 years	Monovalent, live-attenuated lamb G10 P[12] strain	Lanzhou Institute of Biological Products, China	2000 (China), nationally licenced
Rotavin-M1	2 doses Minimum 6 weeks given at least 30 days apart	Monovalent, live-attenuated human G1 P[8] strain	Polyvac, Vietnam	2007 (Vietnam), nationally licenced

LLR: Lanzhou lamb rotavirus

Appendix 9. Detailed search strategies

Search number	Pubmed Query
1	rotavirus vaccin*[Title/Abstract]
2	"Rotavirus Vaccines"[Mesh] OR "rotavirus vaccine 89-12" [Supplementary Concept] OR "rhesus rotavirus vaccine" [Supplementary Concept] OR "RotaTeq" [Supplementary Concept] OR "WC3 rotavirus vaccine" [Supplementary Concept] OR "RV3 rotavirus vaccine" [Supplementary Concept] OR "Romovac 50" [Supplementary Concept] OR "RIT 4237 vaccine" [Supplementary Concept]

(Continued)

3	Rotarix or RIX4414 or Rotateq or wc3 or RV5
4	rotavac or rotavax or BRV-PV or "rotavirus pentavalent vaccine"
5	Rotavin or Polyvac
6	"Lanzhou Institute of Biological Products"
7	rotasil or rotasiil
8	rotavirus AND "Serum Institute of India"
9	(((((((rotavirus AND "Serum Institute of India") OR (rotasil or rotasiil)) OR ("Lanzhou Institute of Biological Products")) OR (Rotavin or Polyvac)) OR (rotavac or rotavax or BRV-PV or "rotavirus pentavalent vaccine")) OR (Rotarix or RIX4414 or Rotateq or wc3 or RV5)) OR ("Rotavirus Vaccines"[Mesh] OR "rotavirus vaccine 89-12" [Supplementary Concept] OR "rhesus rotavirus vaccine" [Supplementary Concept] OR "RotaTeq" [Supplementary Concept] OR "WC3 rotavirus vaccine" [Supplementary Concept] OR "RV3 rotavirus vaccine" [Supplementary Concept] OR "Romovac 50" [Supplementary Concept] OR "RIT 4237 vaccine" [Supplementary Concept])) OR (rotavirus vaccin*[Title/Abstract])
10	(((((((rotavirus AND "Serum Institute of India") OR (rotasil or rotasiil)) OR ("Lanzhou Institute of Biological Products")) OR (Rotavin or Polyvac)) OR (rotavac or rotavax or BRV-PV or "rotavirus pentavalent vaccine")) OR (Rotarix or RIX4414 or Rotateq or wc3 or RV5)) OR ("Rotavirus Vaccines"[Mesh] OR "rotavirus vaccine 89-12" [Supplementary Concept] OR "rhesus rotavirus vaccine" [Supplementary Concept] OR "RotaTeq" [Supplementary Concept] OR "WC3 rotavirus vaccine" [Supplementary Concept] OR "RV3 rotavirus vaccine" [Supplementary Concept] OR "Romovac 50" [Supplementary Concept] OR "RIT 4237 vaccine" [Supplementary Concept])) OR (rotavirus vaccin*[Title/Abstract])
11	(randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type])
12	randomized[Title/Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]
13	drug therapy [subheading]
14	((drug therapy [subheading]) OR (randomized[Title/Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract])) OR ((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type]))
15	(((drug therapy [subheading]) OR (randomized[Title/Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract])) OR ((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type]))) AND (((((((rotavirus AND "Serum Institute of India") OR (rotasil or rotasiil)) OR ("Lanzhou Institute of Biological Products")) OR (Rotavin or Polyvac)) OR (rotavac or rotavax or BRV-PV or "rotavirus pentavalent vaccine")) OR (Rotarix or RIX4414 or Rotateq or wc3 or RV5)) OR ("Rotavirus Vaccines"[Mesh] OR "rotavirus vaccine 89-12" [Supplementary Concept] OR "rhesus rotavirus vaccine" [Supplementary Concept] OR "RotaTeq" [Supplementary Concept] OR "WC3 rotavirus vaccine" [Supplementary Concept] OR "RV3 rotavirus vaccine" [Supplementary Concept] OR "Romovac 50" [Supplementary Concept] OR "RIT 4237 vaccine" [Supplementary Concept])) OR (rotavirus vaccin*[Title/Abstract])

Database: Embase 1947-Present, updated daily

Search Strategy:

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1 Rotavirus vaccine/ or rotavirus vaccin*.mp.

2 Simian rotavirus vaccine/

3 (Rotarix or RIX4414 or Rotateq or wc3 or RV5).mp.

4 (rotavac or rotavax or BRV-PV or "rotavirus pentavalent vaccine").mp.

5 (Rotavin or Polyvac).mp.

6 "Lanzhou Institute of Biological Products".mp.

7 (rotasil or rotasiil).mp.

8 1 or 2 or 3 or 4 or 5 or 6

9 (randomized or randomised or randomly or placebo or double-blind* or single-blind*).tw.

10 randomized controlled trial/ or controlled clinical trial/

11 crossover procedure/

12 9 or 10 or 11

13 8 and 12

Clinicaltrials.gov
rotavirus vaccine
Rotarix
V260
RotaTeq
RIX4414 vaccine
vaccine
Immunization
inoculations
VACCIN
Vaccination
rotavirus

SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH (Web of science)

#3	#2 AND #1 Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years

(Continued)

#2	**TOPIC:** ((randomized trial or clinical trial) OR (crossover or placebo or cohort or double-blind* or single-blind*)) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
#1	**TOPIC:** (("Rotavirus vaccin*") OR (Rotarix or RIX4414 or Rotateq or wc3 or RV5) OR (rotavac or rotavax or BRV-PV or "rotavirus pentavalent vaccine") OR (Rotavin or Polyvac)) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years **LILACS** Rotavirus AND vaccin$ [Words] or Rotarix or RIX4414 or Rotateq or wc3 or RV5 or rotavac or rotavax or BRV-PV or Rotavin or Polyvac [Words] Cochrane Central Register of Controlled Trials Issue 11 of 12, November 2020 #1 Rotarix or RIX4414 or Rotateq or wc3 or RV5:ti,ab,kw or rotavac or rotavax or BRV-PV or "rotavirus pentavalent vaccine" #2 Rotavin or Polyvac #3 "Lanzhou Institute of Biological Products" #4 MeSH descriptor: [Rotavirus Vaccines] explode all trees #5 rotavirus and vaccin* #6 rotasil or rotasiil #7 #1 or #2 or #3 or #4 or #5 or #6

WHO ICTRP: rotavir* and vaccine

WHAT'S NEW

Date	Event	Description
4 November 2021	New search has been performed	This is the fifth update of the original rotavirus vaccines review (Soares-Weiser 2004). This review concerns vaccines that have been prequalified for global use by the WHO (WHO 2021a). In the previous versions of this review, we included any rotavirus vaccine in use (Soares-Weiser 2004; Soares-Weiser 2010; Soares-Weiser 2012a; Soares-Weiser 2012b). New pre-approved methods for the 2021 update are detailed in Table 1) and 'Differences between protocol and review' section.
4 November 2021	New citation required and conclusions have changed	The current update of the review includes 60 independent trials (see Characteristics of included studies), five of which are new to this update (SIIL Isanaka 2017-NER; SIIL Kulkarni 2017-IND; SIIL Zade 2014-INDa; SIIL Zade 2014-INDb; SIIL Zade 2014-INDc).

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 5, 2010

Date	Event	Description
21 October 2019	New citation required but conclusions have not changed	The review author team made two amendments to the review text, in response to the comments submitted by V Singh and B Benninghoff.
21 October 2019	Amended	In response to comments submitted on the Cochrane Library by V Singh and B Benninghoff, the review author team made two amendments to the Methods and Implications for practice sections.
19 March 2019	New citation required but conclusions have not changed	This is the fourth update of the original rotavirus vaccines review (Soares-Weiser 2004). This review concerns vaccines that have been prequalified for global use by the WHO (WHO 2021a). In the previous versions of this review we included any rotavirus vaccine in use.
19 March 2019	New search has been performed	We amended the protocol to include only vaccines prequalified for use by the World Health Organization (WHO). We included 14 new studies from the April 2018 search, including four studies on a new vaccine (Rotavac). Nicholas Henschke joined the author team.
10 May 2012	New citation required but conclusions have not changed	Review updated to incorporate different country mortality strata and outcomes changed to reflect the different rotavirus vaccines' efficacy and safety in countries with different mortality rates.
10 May 2012	New search has been performed	No new trials were identified from the updated May 2012 search.
8 January 2012	New search has been performed	Review updated to include nine trials identified in a new literature search, which was conducted in October 2011 (MEDLINE via PubMed) and June 2011 (other databases).
11 November 2011	New citation required but conclusions have not changed	Hanna Bergman and Sukkrti Nagpal joined the author team.
10 May 2010	Amended	Minor typographical errors corrected.
2 February 2010	New citation required and conclusions have changed	A new search on 2 February 2010 identified 9 new potentially relevant studies. We independently assessed these studies and incorporated data from the eligible trials into the review.
21 July 2009	New search has been performed	The original rotavirus vaccines review (Soares-Weiser 2004) was split into two reviews: rotavirus vaccines in use (this review); and other rotavirus vaccines, including those no longer in use or in development (Soares-Weiser 2004). This involved a new search, revised inclusion criteria, updated review methods. All data from those trials also included in the original review were re-extracted. New authors joined the review team for this review.

CONTRIBUTIONS OF AUTHORS

Hanna Bergman: created summary of findings tables, screened references, extracted input and analysed data, including risk of bias assessments, and updated the review text for the 2012, 2019, and this review update.

Nigel Cunliffe: provided guidance on inclusion criteria, review structure and content. He updated the Background and Discussion sections, and commented on summary of findings tables and review drafts for the 2012, 2019, and this review update.

Nicholas Henschke: screened abstracts and full texts, extracted and analysed data, assessed risk of bias, and reviewed summary of findings tables and the manuscript for the 2019 and this review update.

Daniel Hungerford: provided guidance on inclusion criteria, review structure and content. He updated the Background and Discussion sections, and commented on summary of findings tables and review drafts for the 2019 and this review update.

Duduzile Ndwandwe: provided guidance on changes for the 2021 review update and commented on review drafts.

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

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

DECLARATIONS OF INTEREST

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

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

Daniel Hungerford received research grant support from GlaxoSmithKline Biologicals and Sanofi Pasteur and Merck and Co after the closure of Sanofi Pasteur-MSD in December 2016.

Duduzile Ndwandwe has no financial interest nor any competing interest in this work.

Femi Pitan has no financial interest nor any competing interest in this work.

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

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

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Internal sources

- Liverpool School of Tropical Medicine, UK

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This is the fifth update of the original rotavirus vaccines review (Soares-Weiser 2004). This review concerns vaccines that have been prequalified for global use by the WHO (WHO 2021a). In the previous versions of this review, we included any rotavirus vaccine in use (Soares-Weiser 2004; Soares-Weiser 2010; Soares-Weiser 2012a; Soares-Weiser 2012b).

New to the 2019 update: we used a random-effects model for all outcomes. Previously a fixed-effect model was used, unless we found statistically significant heterogeneity ($P < 0.10$) for a specific outcome, in which case we used the random-effects model.

New pre-approved methods for the 2021 update included (Table 1):

- Rotavirus diarrhoea outcomes were collected for the second year of life in addition to previously collected time points.
- Data were stratified by low-, medium-, and high-mortality countries using UNICEF under-five child mortality rates from 2019.
- We did not collect and report on immunogenicity outcomes; sufficient efficacy data are available for all four vaccines.

New post hoc subgroup analysis to the 2021 update: intussusception is a very rare event; to get a more stable estimate, we presented analyses for the risk of intussusception with any vaccine compared with placebo by country-mortality setting and overall in an additional table.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Child; Child, Preschool; Humans; Infant; Infant, Newborn; Young Adult