Rotavirus Vaccines Schedules: A systematic review of safety and efficacy from randomized controlled trials and observational studies of childhood schedules using RV1 and RV5 vaccines

REPORT TO WHO/IVR

Karla Soares-Weiser (MD, PhD)

Enhance Reviews Ltd

AVAILABLE EVIDENCE COMPARING DIFFERENT SCHEDULES OF ROTAVIRUS VACCINES FOR CHILDREN LIVING IN DIFFERENT MORTALITY STRATA SETTINGS

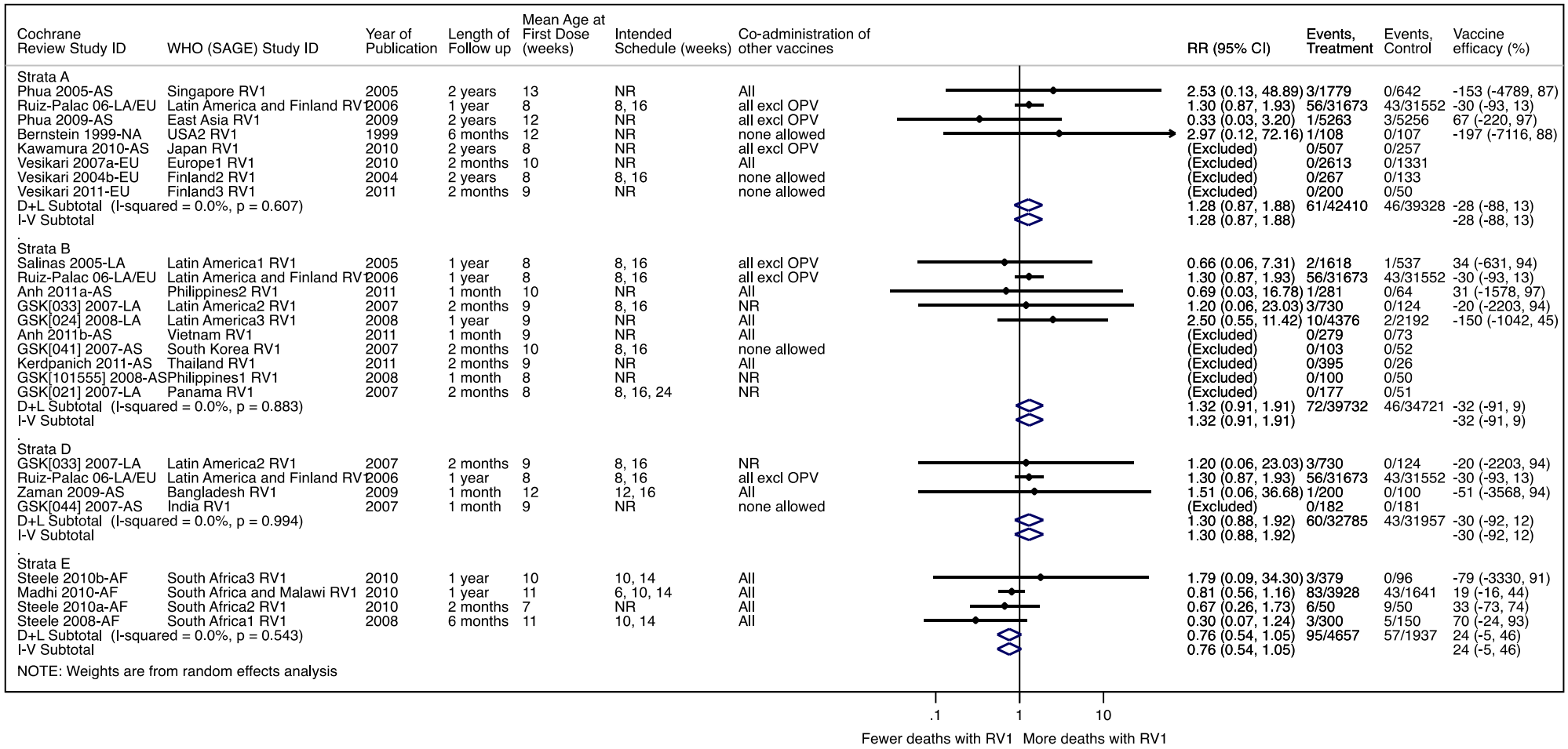
1. IMPACT OF CURRENT ROTAVIRUS VACCINE IMMUNIZATION SCHEDULES COMPARED TO ALTERNATIVE SCHEDULES ON RELEVANT OUTCOMES

A. MORTALITY

Limited data from historical-control studies of RV1 suggest a reduction in diarrhoea mortality two years after vaccine implementation in three Latin American countries (Strata B and D). Data from RCTs show no statistically significant difference on all-cause mortality between different vaccine schedules or among studies in different WHO mortality strata.

- **Overall effect:**
  - Twenty-two RCTs of RV1 and six RCTs of RV5 reported on all-cause mortality. Death was a rare event in these RCTs and no statistically significant difference was found in the number of deaths observed among children receiving RV vaccines or placebo for mortality strata A, B, D, and E. However, these RCTs were not powered to assess mortality and in 12 of these RCTs data on mortality was reported for less than 2 months after vaccine administration.
  - Three historical-control studies from Latin America (Stratum B) with high vaccine coverage reported a 42% relative reduction on diarrheal mortality in children less than one year old, two years after RV1 introduction when compared to observed diarrheal mortality during two to three years before vaccine introduction. However, data were only pooled for 2008 and no specific details on schedule were provided for these studies.
- **Number of doses:** A single RCT in Africa (Stratum E) comparing three and two doses of RV1 reported no statistically significant difference in mortality. No observational studies that reported on mortality compared different number of doses.
- **Age at first dose:** Three RCTs compared different ages at first vaccine dose, but reported no statistically significant differences in mortality. Indirect comparisons based on stratification of RV1 and RV5 RCTs using different schedules showed no impact on mortality for different ages at first dose. No observational studies compared different age at first dose.
- **Interval between doses:** Two RCTs compared different intervals between doses, but reported no statistically significant differences in mortality. Indirect comparisons based on stratification of RV1 and RV5 RCTs using different schedules showed no impact on mortality for different intervals between doses. No observational studies compared different intervals between doses.
- **Concomitant use of other childhood vaccines:** Two RCTs comparing concomitant use of oral polio vaccine with RV1 vs. RV1 alone or with inactivated polio vaccine showed no impact on mortality. One small RCT comparing RV5+OPV with RV5 alone also showed no impact on mortality. Indirect comparisons based on stratification of RV1 and RV5 RCTs showed no significant impact on mortality for RCTs 1) in which all vaccines were allowed, 2) RCTs that did not allow concomitant use of polio vaccine (OPV or IPV) or 3) RCTs that did not allow concomitant use of any other childhood vaccines. No observational studies compared different schedules of co-administration of other childhood vaccines.

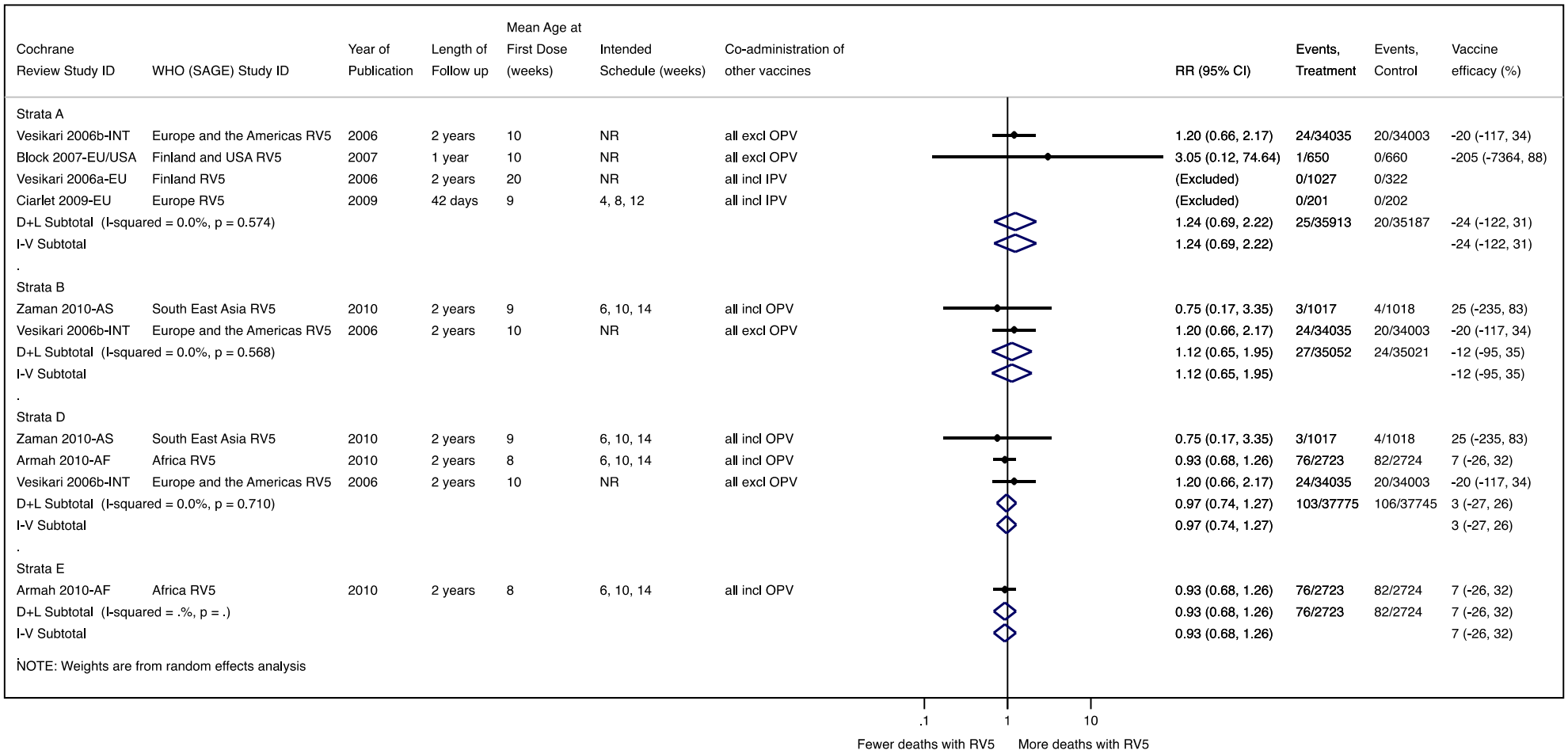
FIGURE I: RCTS OF RV1 VS. PLACEBO – ALL CAUSE MORTALITY AFTER ROTAVIRUS VACCINATION STRATIFIED ACCORDING TO WHO MORTALITY STRATA



Legend Figure I:

Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Studies stratified according to the World Health Organization list of member states by mortality stratum (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). Two multi-centric trials were performed in more than one region and contributed to more than one stratum.(2, 3) All children in *South Africa2 RV1*(4) and part of children in *South Africa and Malawi RV1*(5) were HIV positive.Horizontal axis represents effect estimate comparing groups of children receiving RV1 vs. placebo; vertical line through 1 shows no difference in mortality between groups; effect estimate might differ between studies depending on data provided in trial report. Black diamonds represent point estimates of risk ratios combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of RV1 (fewer deaths with RV1), points to the right of the line show a detrimental effect of RV1 (more deaths with RV1); I^2 value is the level of statistical heterogeneity between trials. CI=confidence interval; NR=not reported; OPV=oral polio vaccine; RR=risk ratio

FIGURE II: RCTS OF RV5 VS. PLACEBO – ALL CAUSE MORTALITY AFTER ROTAVIRUS VACCINATION STRATIFIED ACCORDING TO WHO MORTALITY STRATA



Legend Figure II:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Studies stratified according to the World Health Organization list of member states by mortality stratum (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). Two multi-centric trials were performed in more than one region and contributed to more than one stratum.(6, 7) Horizontal axis represents effect estimate comparing groups of children receiving RV5 vs. placebo; vertical line through 1 shows no difference in mortality between groups; effect estimate might differ between studies depending on data provided in trial report. Black diamonds represent point estimate of risk ratios combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of RV5 (fewer deaths with RV5), points to the right of the line show a detrimental effect of RV5 (more deaths with RV5); I^2 value is the level of statistical heterogeneity between trials. CI=confidence interval; IPV=inactivated polio vaccine; NR=not reported; OPV=oral polio vaccine; RR=risk ratio

A.1. Summary of results

A.1.1. Effect of rotavirus vaccine on all-cause mortality by mortality strata

Twenty-two RCTs of RV1(2-5, 8-25) and six of RV5(6, 7, 26-29) were performed in strata A, B, D, and E and showed no statistically significant impact on mortality, and no differences were observed within strata on the number of deaths in children (Figures 1 and 2).

One study from Brazil(30), compared mortality before and after introducing RV1 vaccine and reported a decline in all-cause mortality among children ≤ 1 year, and no difference in children 2-4 years (Table A-V).(30)

The current evidence is limited by the fact that the included RCTs were not powered to assess mortality, 12 of these RCTs were designed only reported data on mortality for less than 2 months after vaccine administration. Only one study was performed after RV1 implementation in Brazil.

A.1.2. Effect of rotavirus vaccine on diarrhoea mortality by mortality strata

Three historical-control studies(30-32) performed in stratum B (Latin America) showed a 42% relative risk reduction on the number of deaths due to diarrheal diseases in children less than one year old and from 24 to 54% in children one to four years old in 2008, two years after RV1 implementation. Another historical-control study from Nicaragua (Stratum D) showed no impact of RV5 on diarrheal mortality(33). For these studies diarrhoea-related mortality estimated for two to three years after rotavirus vaccination (2007–2009) was compared to expected rates calculated from pre-vaccine years (2002–2005); we analyzed data for 2008 as data for this year was provided for all studies. Although no specific information was provided about schedules for these studies, each country's policy was to administer RV1 with other vaccines on schedule and recommended administration of the RV1 vaccine at 2 and 4 months of age (Table A-VI). Hence, the current evidence is weak, and based on four historical control studies performed only in Latin American countries (strata B and D).

A.1.3. Effect of different number of doses of rotavirus vaccine on mortality

Weak evidence from a single RCT (South Africa3 RV1(21)), reported a non-statistically significant difference on mortality after 6 months of follow up comparing three and two doses of RV1. In this trial one child receiving three doses of RV1 and two children receiving two doses of RV1 died (RR 0.50, 95%CI 0.05-5.50, N=379). This trial was designed to measure vaccine immunogenicity; RV1 and placebo were given in a 6-10-14 weeks schedule, and all other vaccines were allowed concomitantly with RV1 (Table A-I). No clinical data from RCTs for RV5 or from observational studies of RV1 and RV5 are available that directly compare different doses.

A.1.4. Effect of age at first dose and interval between doses on mortality

Three RCTs of RV1 vaccine (Philippines2 RV1(8), South Africa1 RV1(20), South Africa3 RV1(21)) reported on mortality one to 12 months of follow up by directly comparing children receiving the first dose of the vaccine at 6-7 weeks of age with children receiving the first dose at 10-11 weeks of age. No significant difference was reported, with 6 of 513 children 6-7 weeks of age and 1 of 447 child 10-11 weeks dying during the trials' follow up period (RR 2.82, 95%CI 0.56-14.04) (Table A-II). Two of these three trials were designed to measure vaccine immunogenicity only(8, 20), RV1 and placebo were given in a 6-10-14 weeks schedule and all other vaccines were allowed concomitantly with RV1 for the South African trials (Table A-II).

Two immunogenicity RCTs (Philippines2 RV1(8), Vietnam RV1(8)) reported on mortality after one month of follow up and directly compared children receiving two doses of RV1 vaccine in different intervals (four or eight weeks interval). A single death was reported in a child given the vaccine with a four weeks interval between doses (RR 2.94, 95%CI 0.12-71.49, N=560) (Table A-III).

No clinical data from RCTs of RV5 or from observational studies of RV1 and RV5 are available that directly compare different age at first dose or different intervals. In addition to the information from the three small RCTs reported above, indirect comparisons from stratification of RV1 and RV5 RCTs using different vaccine schedules (age of children receiving the first dose of RV1 or RV5 and interval between doses) was analysed; pooled data have not shown any significant difference in the reported number of deaths in children receiving vaccine or placebo (Table A-V).

The current evidence is weak, based on direct comparison of three small RV1 RCTs not powered to observe an effect on mortality, and on stratification of RCTs not designed to measure a difference between different vaccine schedules, and also not powered to observe an effect on mortality.

A.1.5. Effect of rotavirus vaccine while given simultaneously with other vaccines on mortality

Two RV1 RCTs directly compared rotavirus vaccines given simultaneously with other childhood vaccines. *South Africa1 RV1*(20) compared children vaccinated with RV1 and oral polio vaccine (OPV) with children receiving RV1 without OPV, all children were also vaccinated with Bacille Calmette-Guerin vaccine (BCG), Diphteria-Tetanus-acellular Pertussis (DPT) and Hepatitis B vaccines. This RCT reported no impact on mortality, with one death among 150 children vaccinated with RV1 and oral polio vaccine (OPV) and two deaths among 150 children vaccinated with RV1 without OPV. *Bangladesh RV1*(25) compared a group of children vaccinated with RV1 and inactivated polio vaccine (IPV) with a group of children randomized to RV1 and OPV, and did not find any significant impact on mortality with a single death reported in the group of children randomized to RV1 and inactivated polio vaccine (IPV) (Table A-IV). All children in this study were also vaccinated with Diphteria-Tetanus-acellular Pertussis and Hepatitis B vaccines.

One RV5 RCT, *Latin America RV5*(34) compared children vaccinated with RV5 and oral polio vaccine (OPV) with children receiving RV5 without OPV, all children were also vaccinated with Diphteria-Tetanus-acellular Pertussis (DPT) and Hepatitis B vaccines. This RCT reported no impact on mortality, with one death among 372 children vaccinated with RV5 and oral polio vaccine (OPV) and one death among 363 children vaccinated with RV5 without OPV (Table A-IV).

In addiction, indirect comparisons from stratification of RV1 and RV5 RCTs reporting different vaccine schedules regarding concomitant administration of other childhood vaccines have not shown any significant difference in the reported number of deaths in children receiving vaccine or placebo (Table A-V). Hence, the current evidence is weak, based only on stratification of RCTs not designed to measure a difference between different vaccine schedules, and not powered to observe an effect on mortality.

A.2. Policy implications of these findings

Randomized trials evaluating RV1 and RV5 were not primarily designed to evaluate mortality, and more than 50% of the studies reported mortality only during the first 2 months after vaccination. As a result, most trials lack precision to examine the impact of RV1 and RV5 on mortality with different schedules.

In three stratum B Latin American countries (Brazil, Mexico and Panama) a 42% reduction in mortality due to diarrhea was observed in children ≤1 year of age and 24 to 54% in children aged 1-4 years two years after implementation of RV1. However, data was only pooled for 2008 and no specific details on schedule was provided in these studies, although it can be assumed that children received RV1 at 2-4 months of age together with other vaccines.

As it is unlikely that RCTs will have the power to detect a difference in all-cause or diarrhoeal mortality between groups, future studies evaluating the impact of the vaccines on mortality after vaccine implementation, in particular in countries from strata D and E, are needed. In addition, there is a need for RCTs designed specifically to measure a difference between different vaccine schedules, in particular, whether adding a third dose of RV1 would have any impact on childhood all-cause or diarrhoeal mortality.

B. SEVERE ROTAVIRUS GASTROENTERITIS

Data from RCTS show that RV1 and RV5 are more efficacious against severe rotavirus gastroenteritis in countries of WHO mortality strata A and B, although they are also efficacious in strata D and E. Data from case-control studies show that RV1 and RV5 are more efficacious when the full schedule is given, but also somewhat efficacious in children receiving only a partial schedule. There is currently very weak evidence from RCTs to make a recommendation on a booster shot of RV1.

Overall effect:

- Eleven RCTs of RV1 and six RCTs of RV5 provided data on severe rotavirus gastroenteritis after one and/or two years follow up. Both vaccines were efficacious in all strata, although a clear gradient can be seen, ranging from approximately 90% in stratum A to 60% in stratum E.

Number of doses:

- Two RCTs comparing three to two doses of RV1 with placebo provided data on severe rotavirus gastroenteritis. Direct comparison of three and two doses showed no statistically significant difference at one year follow up. The second year follow up of the *South Africa and Malawi* RCT, using only the Malawi cohort, showed a non-significant higher vaccine efficacy when a third dose of RV1 vaccine was added.
- Three case-control and one historical control study reported data for RV1 on rotavirus diarrhoea related healthcare encounters for different number of doses administered; an indirect comparison showed a trend for the effect size to increase with increasing number of doses**.** Five case-controls and three historical control studies reporting data for RV5 on rotavirus diarrhoea related healthcare encounters were pooled, showing a trend for the effect size to increase with increasing number of doses.

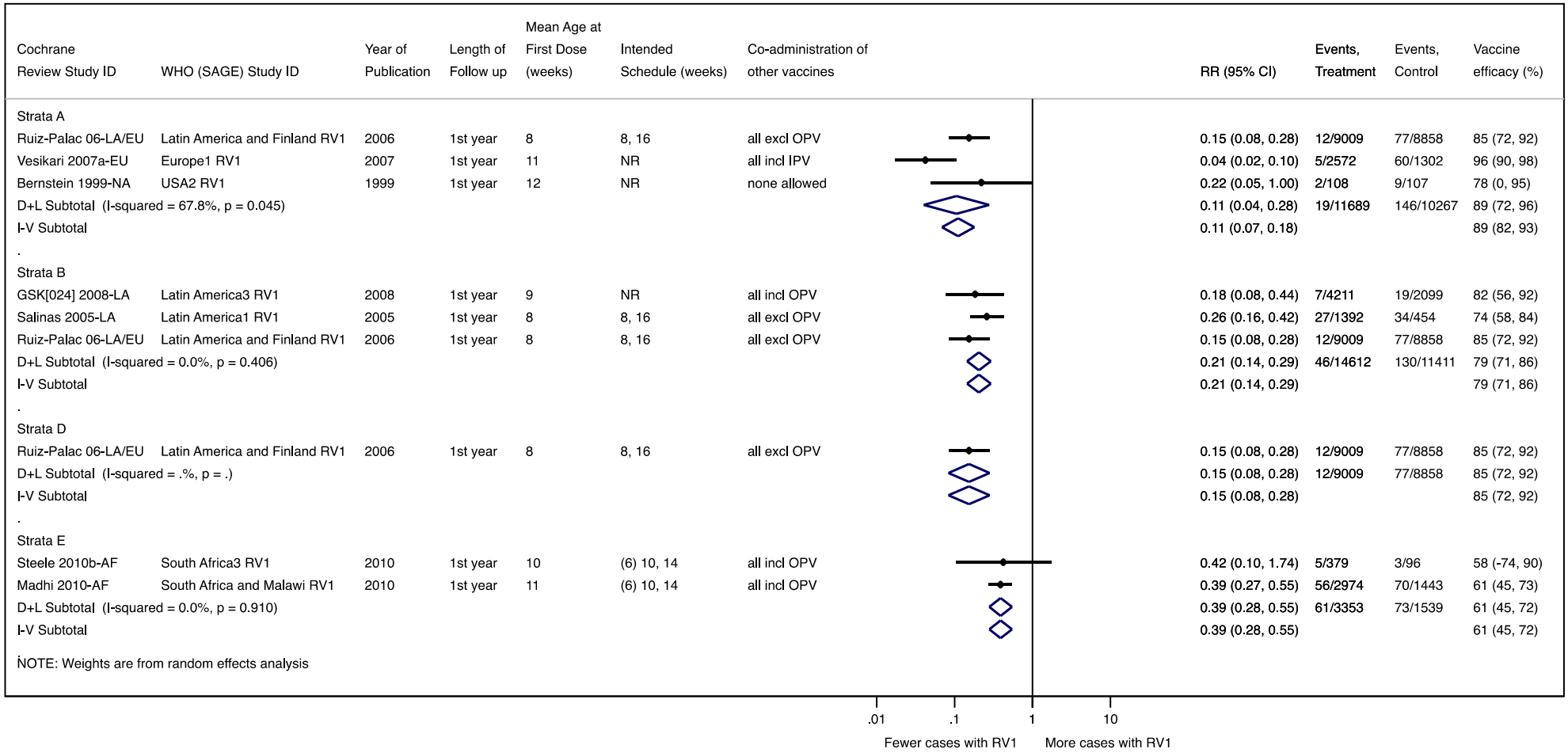
Age at first dose and interval between doses:

- Two RCTs reported data on severe rotavirus gastroenteritis up to one year follow up. Direct comparison of receiving the first dose between 6 vs. 10-11 weeks of age showed no statistically significant difference. The second year follow up of the *South Africa and Malawi* RCT, using only the Malawi cohort, also showed no statistically significant difference between these dosing schedules.
  Indirect comparisons based on stratification of RV1 and RV5 trials using different schedules showed efficacy against severe rotavirus gastroenteritis for various ages at first dose and for intervals of 4- 10 weeks between doses.

Concomitant use of other childhood vaccines:

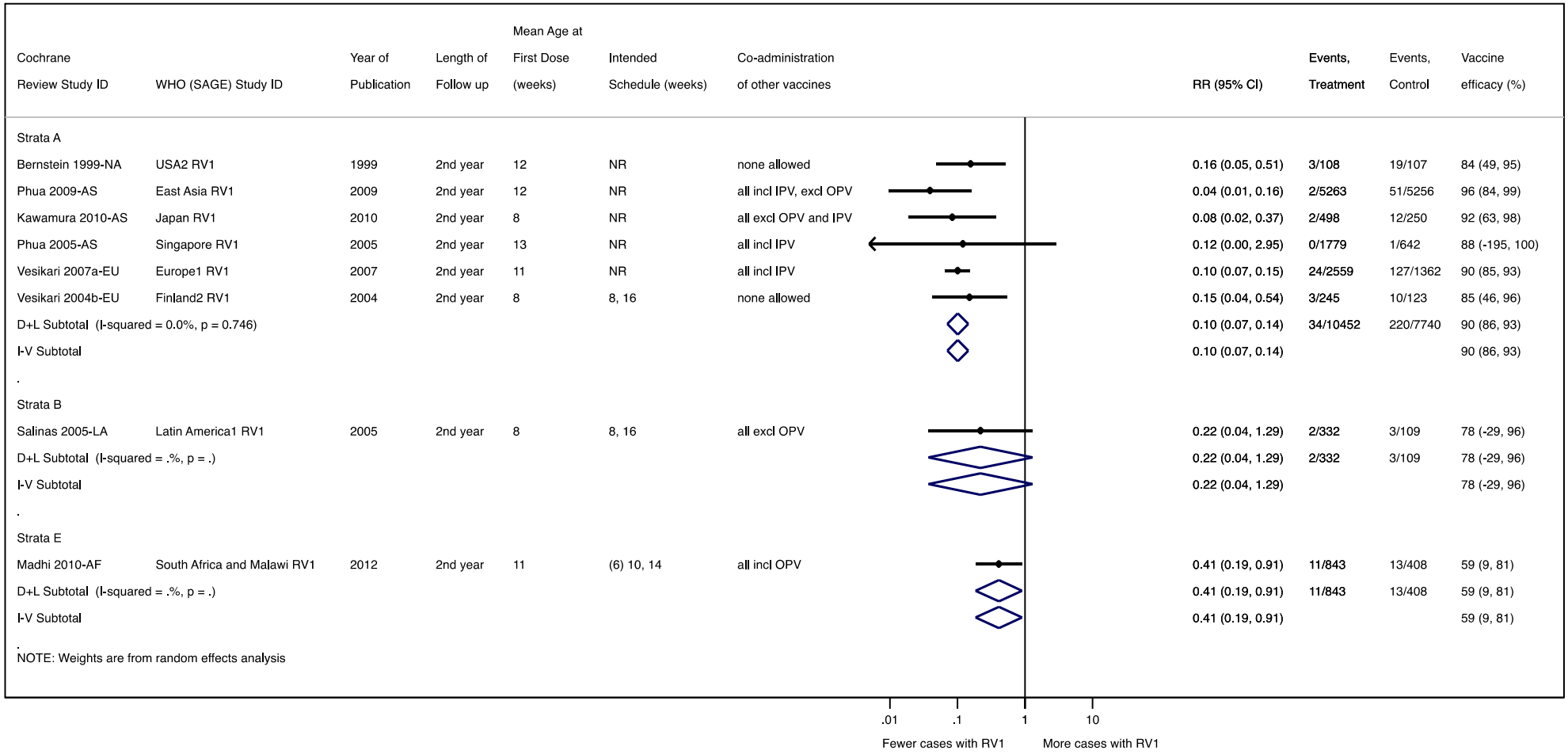
- Indirect comparisons from stratification of RV1 and RV5 RCTs grouped as to whether concomitant administration of rotavirus vaccines was allowed with any other vaccine (including OPV), any other vaccine including IPV (with the assumption that OPV was excluded, although this was not reported), any other vaccine excluding OPV, or no other vaccine was allowed have not shown a significant impact of vaccine co-administration on the rotavirus vaccines efficacy against severe rotavirus gastroenteritis compared to placebo, except for except for one trial of RV5 (*Finland and USA RV5*, stratum A) in which OPV was not allowed within two weeks of RV5 vaccination. No pattern was seen in the data and this finding might be due to the small sample size of this RCT.

FIGURE III: RCTS OF RV1 VS. PLACEBO – ROTAVIRUS VACCINE EFFECT ON SEVERE ROTAVIRUS GASTROENTERITIS WITH LESS THAN ONE YEAR OF FOLLOW UP STRATIFIED ACCORDING TO WHO MORTALITY STRATA



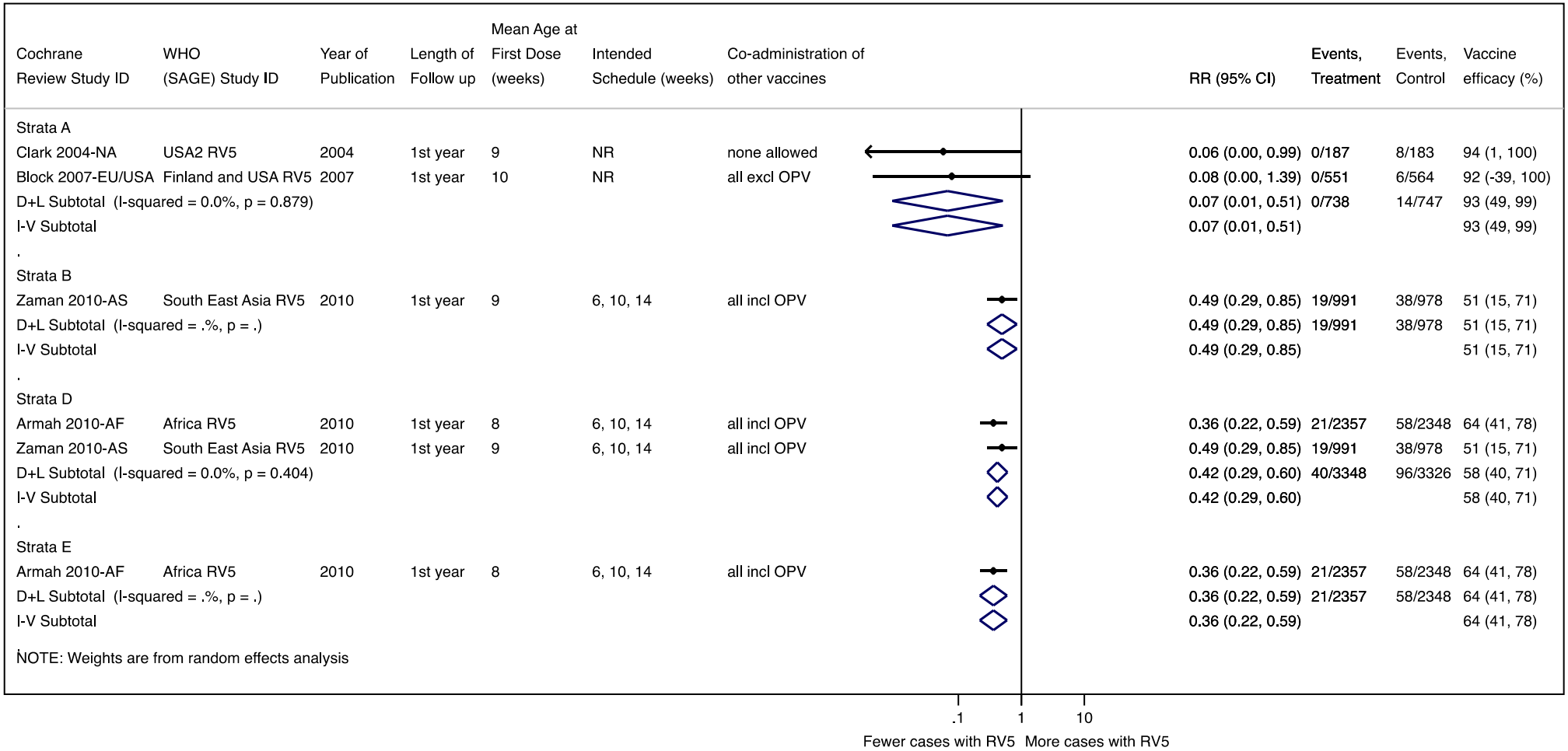
Legend Figure III:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Studies stratified according to the World Health Organization list of member states by mortality stratum (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). One multi-centric trial was performed in more than one region and contributed to more than one stratum.(3) Some of the children in *South Africa and Malawi RV1* were HIV positive.(5) Children on *South Africa and Malawi RV1*and *South Africa3 RV1* were randomised to 2 or 3 doses of RV1 vs. placebo, children receiving 3 doses start vaccination at 6 weeks of age.(5, 21) Horizontal axis represents effect estimate comparing groups of children receiving RV1 vs. placebo; vertical line through 1 shows no difference in severe rotavirus gastroenteritis (RVGE) up to one year follow up between groups; effect estimate might differ between studies depending on data provided in the trial reports. Black diamonds represent point estimate of risk ratio combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of RV1 (fewer cases with RV1), points to the right of the line show a detrimental effect of RV1 (more cases with RV1); I^2 value is the level of statistical heterogeneity between trials. CI=confidence interval; NR=not reported; OPV=oral polio vaccine; RR=risk ratio, RVGE=rotavirus gastroenteritis

FIGURE IV: RCTS OF RV1 VS. PLACEBO – ROTAVIRUS VACCINE EFFECT ON SEVERE ROTAVIRUS GASTROENTERITIS WITH UP TO TWO YEARS FOLLOW UP STRATIFIED ACCORDING TO WHO MORTALITY STRATA



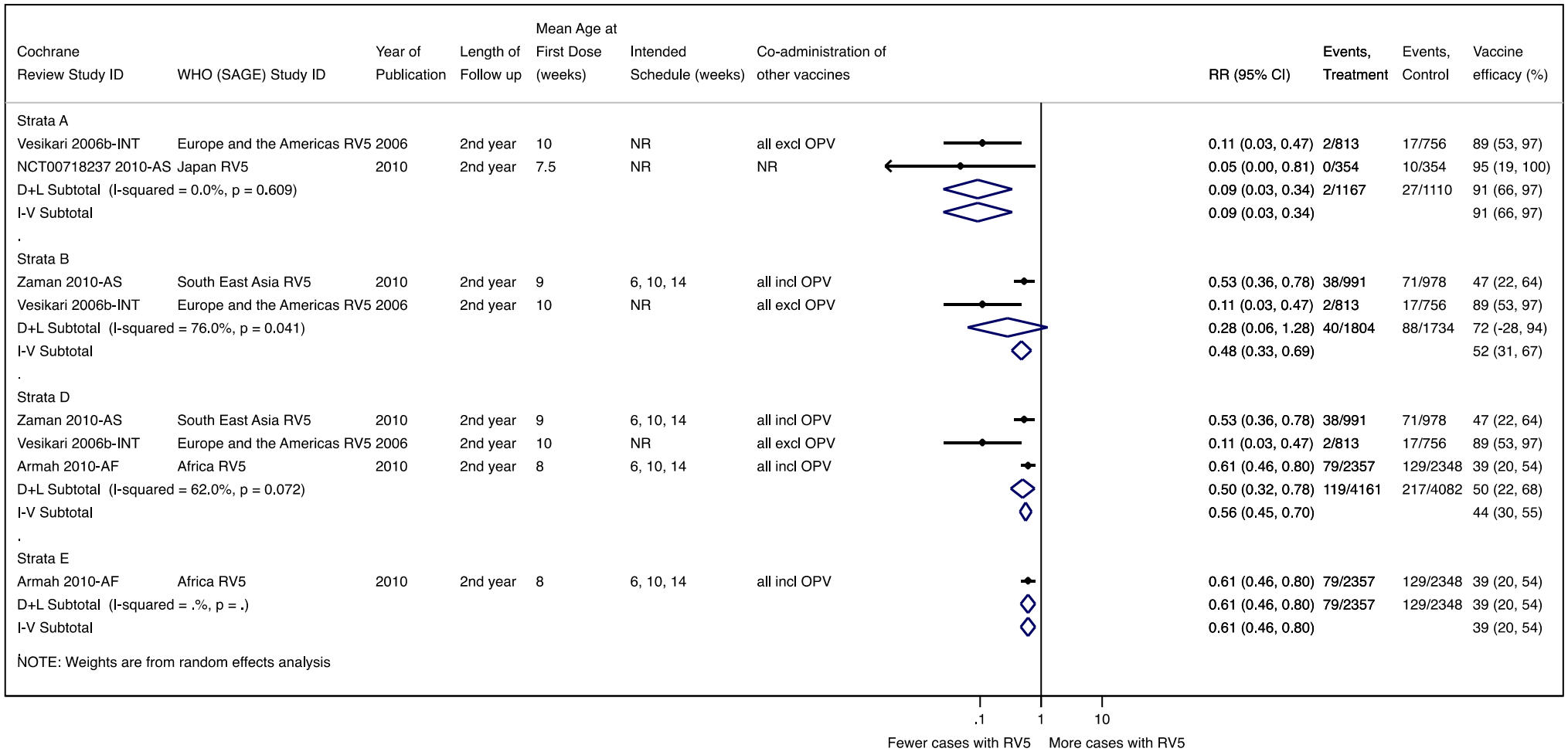
Legend Figure IV:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Studies stratified according to the World Health Organization list of member states by mortality stratum (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). Some of the children in *South Africa and Malawi RV1* were HIV positive, and only the cohort from Malawi was followed up for the second year.(5, 35)Children on *South Africa and Malawi RV1*were randomised to 2 or 3 doses of RV1 vs. placebo, children receiving 3 doses start vaccination at 6 weeks of age.(5) Data for the second year follow up for *Latin America1 RV1*and *South Africa and Malawi RV1*was reported only for a sub-sample of children.(35, 36)Horizontal axis represents effect estimate comparing groups of children receiving RV1 vs. placebo; vertical line through 1 shows no difference in severe RVGE upCENTER to one year follow up between groups; effect estimate might differ between studies depending on data provided in trial report. Black diamonds represent point estimate of risk ratio combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of RV1 (fewer cases with RV1), points to the right of the line show a detrimental effect of RV1 (more cases with RV1); I^2 value is the level of statistical heterogeneity between trials. CI=confidence interval; NR=not reported; OPV=oral polio vaccine; IPV=inactivated polio vaccine; RR=risk ratio, RVGE=rotavirus gastroenteritis

FIGURE V: RCTS OF RV5 VS. PLACEBO – ROTAVIRUS VACCINE EFFECT ON SEVERE ROTAVIRUS GASTROENTERITIS WITH LESS THAN ONE YEAR OF FOLLOW UP STRATIFIED ACCORDING TO WHO MORTALITY STRATA



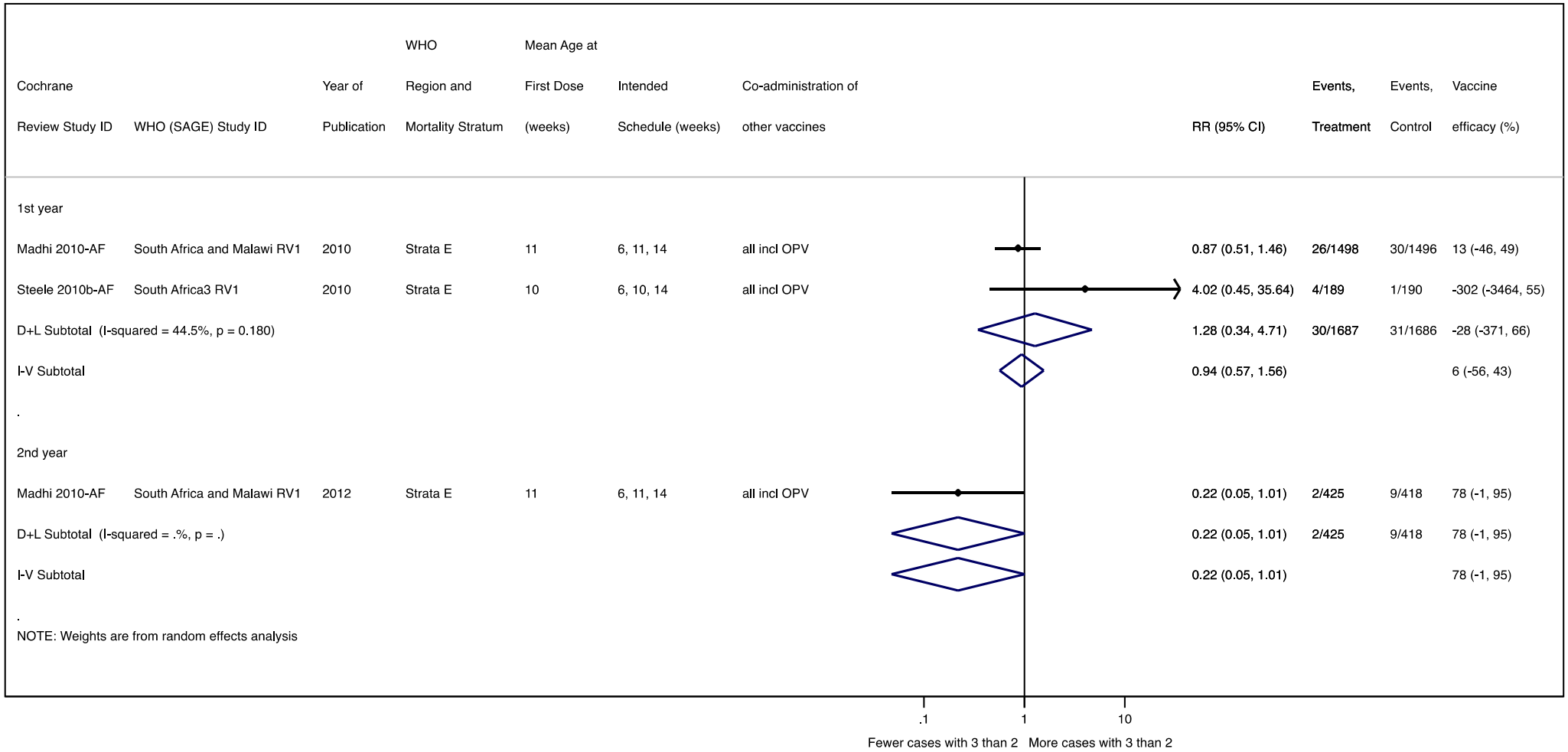
Legend Figure V:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Studies stratified according to the World Health Organization list of member states by mortality stratum (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). Two multi-center RCTs were performed in more than one region and contributed to more than one stratum.(6, 29) Horizontal axis represents effect estimate comparing groups of children receiving RV5 vs. placebo; vertical line through 1 shows no difference in severe rotavirus gastroenteritis between groups; effect estimate might differ between studies depending on data provided in trial report. Black diamonds represent point estimate of risk ratio combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of RV5 (fewer cases with RV5), points to the right of the line show a detrimental effect of RV5 (more cases with RV5); I^2 value is the level of statistical heterogeneity between trials.CI=confidence interval; IPV=inactivated polio vaccine; NR=not reported; OPV=oral polio vaccine; RR=risk ratio

FIGURE VI: RCTS OF RV5 VS. PLACEBO – ROTAVIRUS VACCINE EFFECT ON SEVERE ROTAVIRUS GASTROENTERITIS WITH UP TO TWO YEARS FOLLOW UP STRATIFIED ACCORDING TO WHO MORTALITY STRATA



Legend Figure VI:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Studies stratified according to the World Health Organization list of member states by mortality stratum (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). Three multi-center RCTs were performed in more than one region and contributed to more than one stratum.(6, 7, 29) Data for *Japan RV5* were extracted from clinicaltrials.gov and entered as the number of children randomised.(37) Horizontal axis represents effect estimate comparing groups of children receiving RV5 vs. placebo; vertical line through 1 shows no difference in severe rotavirus gastroenteritis between groups; effect estimate might differ between studies depending on data provided in trial report. Black diamonds represent point estimate of risk ratio combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of RV5 (fewer cases with RV5), points to the right of the line show a detrimental effect of RV5 (more cases with RV5); I^2 value is the level of statistical heterogeneity between trials.CI=confidence interval; IPV=inactivated polio vaccine; NR=not reported; OPV=oral polio vaccine; RR=risk ratio

FIGURE VII: RCTS COMPARING THREE DOSES OF RV1 VS. TWO DOSES OF RV1 ROTAVIRUS VACCINE - EFFECT ON SEVERE ROTAVIRUS GASTROENTERITIS



Legend Figure VII:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1)Second year follow up was reported only for the Malawi cohort on the *South Africa and Malawi RV1* trial.(5)Horizontal axis represents effect estimate comparing groups of children receiving 3 vs 2 doses of RV1; vertical line through 1 shows no difference in severe rotavirus gastroenteritis between groups; effect estimate might differ between studies depending on data provided in trial report. Black diamonds represent point estimate of risk ratio combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of three doses of RV1 (fewer cases with 3 than 2), points to the right of the line show a detrimental effect of three doses of RV1 (more cases with 3 than 2); I^2 value is the level of statistical heterogeneity between trials. CI=confidence interval; IPV=inactivated polio vaccine; NR=not reported; OPV=oral polio vaccine; RR=risk ratio

B.1. SUMMARY OF RESULTS

B.1.1. SEVERE ROTAVIRUS GASTROENTERITIS AFTER ROTAVIRUS VACCINE ADMINISTRATION ACCORDING TO WHO MORTALITY STRATA

Eleven RCTs of RV1 provided data on severe rotavirus gastroenteritis after up to one(3, 9, 11, 19, 21, 23, 35) and/or two years(5, 9, 15, 17-19, 22, 23) of follow up. Trials were performed in strata A, B, D and E and, although RV1 vaccine was highly efficacious in all strata, a clear gradient is observed, with vaccine efficacy varying from 91% in stratum A to 61% in stratum E in RCTs of up to one year follow up (Figure III) and from 90% to 59% in RCTs of up to two years follow up (Figure IV).

Six RCTs on RV5 provided data on severe rotavirus gastroenteritis after up to one (6, 26, 29, 38) and/or two years(6, 7, 29, 37) of follow up. Trials were performed in strata A, B, D and E. RV5 was highly efficacious in stratum A (93% in up to one year and 91% in up to two years follow up), but only moderately efficacious in strata B to E. Data is presented on Figures V and VI. In addition, recently a post-hoc analysis(39) from the REST trial (Europe and the Americas RV5)(7) reported no statistically significant effect against **rotavirus diarrhoea related health care encounters** for children that only received one or two RV5 doses, compared to placebo

Limitations of these analyses are the fact that the four largest studies contributed data to more than one stratum(3, 6, 7, 29), and that three RCTs(5, 7, 36) only followed up a subset of the initial sample during the second year. In addition, observational studies reporting data on severe rotavirus gastroenteritis, but not reporting specific data on different schedules were not included in the current review, therefore no conclusion can be made regarding vaccine efficacy after vaccines had been implemented in different countries.

The current evidence is moderate, based on RCTs performed in strata A, B, D and E.

B.1.2. SEVERE ROTAVIRUS GASTROENTERITIS AFTER ROTAVIRUS VACCINE ADMINISTRATION BY NUMBER OF DOSES GIVEN

Two RCTs(21, 35) provided data on severe rotavirus gastroenteritis with up to one year follow up, comparing three with two doses of RV1. These two trials had three arms, children allocated to three doses of RV1 started vaccination at the age of 6 weeks, and children allocated to two doses started vaccination at 10 to 11 weeks of age, and Direct comparison of three and two doses showed no statistically significant difference (RR 1.28, 95%CI 0.34-4.71, N=3373). The *South Africa and Malawi RV1* trial(5) recently reported efficacy against severe rotavirus gastroenteritis during the second year follow up using only the Malawi cohort. Results showed a non-significant tendency towards greater efficacy with three doses over two doses (RR 0.22, 95%CI 0.05-1.01, N=843) (Figure VII, Table B-I).

One cohort study(40) and eight surveillance studies with historical controls(33, 41-47), and 13 case-control studies(48-60)reported data on **rotavirus diarrhoea related health care encounters** (hospitalization or emergency department visit due to rotavirus diarrhoea) with different number of doses. Three case-control and one historical control study(41, 49, 51, 52), performed in countries from strata A (Australia) and B (Brazil and El Salvador), reported data on children receiving the full schedule (two doses) or a single dose of RV1. An indirect comparison of the effect size did not show obvious differences with either one or two doses (one dose: OR 0.60, 95% CI 0.44 to 0.82, I^2=5%, p=0.368; two doses OR 0.40, 95% CI 0.20 to 0.81, I^2=78.2%, p=0.003) in vaccinated children ≤3 years compared to unvaccinated children (Table B-II). Nine studies from countries in stratum A (Australia and USA)(43, 45, 47, 54-56, 58) and one from stratum D (Nicaragua)(57) reported data following RV5 vaccination. Five case-control and three historical control studies were pooled and there was a trend for the effect size to increase with increasing number of doses (one dose: OR 0.34, 95% CI 0.20 to 0.59, I^2=69.4%, p=0.001; two doses OR 0.24, 95% CI 0.14 to 0.40, I^2=36.4%, p=0.138; three doses OR 0.18, 95% CI 0.11 to 0.29, I^2=62.9%, p=0.003) (Table B-II).

Two additional case-control studies (stratum A) reported data on different doses for rotavirus diarrhoea related health care encounters following national introduction of RV1 or RV5 rotavirus vaccines. One case-control study conducted in the USA reported more than 93% vaccine efficacy for partially vaccinated children (one or two doses) and more than 96% vaccine efficacy for fully vaccinated children (three doses), compared to unvaccinated children.(59) Another case-control study conducted in Israel reported a larger proportion of RV negative children vaccinated with one, two or three doses compared to RV positive children, but no statistical analysis was reported (See Table A4.3 in Appendix). (60)

In summary, although the second year follow up of the *South Africa and Malawi RV1* RCT(5) showed a potential for higher vaccine efficacy when a booster shot of RV1 vaccine was added, currently there is not enough evidence to make a recommendation. It is recommended that further RCTs in countries with high childhood mortality rates (strata D and E) where vaccine efficacy is lower be performed. Observational studies after vaccine implementation evaluating the potential impact of partial vaccination with both RV1 and RV5 in countries from strata D and E should also be recommended.

B.1.3. Severe rotavirus gastroenteritis after rotavirus vaccine administration by age at first dose and interval between doses

Two RCTs(21, 35) reported data on severe rotavirus gastroenteritis with up to one year follow up, and directly compared children receiving the first dose of RV1 at age 6 weeks vs. 10 to 11 weeks. Direct comparison of 6 vs. 10-11 weeks of age showed no statistically significant difference (RR 1.28, 95%CI 0.34-4.71, N=3373). The *South Africa and Malawi RV1* trial(5) recently reported efficacy against severe rotavirus gastroenteritis during the second year follow up using only the Malawi cohort, results were not statistically different for children age 6 compared to children 10 to 11 weeks of age average (RR 0.22, 95%CI 0.05-1.01, N=843).

Except for these two small RV1 RCTs, no clinical data from RCTs of RV5 vaccines or from observational studies of RV1 and RV5 vaccines are available directly comparing details of schedules. Indirect comparisons from stratification of RV1 and RV5 RCTs using different vaccine schedules (age of children receiving the first dose of RV1 or RV5, and interval between doses) have shown most schedules to be efficacious against severe rotavirus gastroenteritis compared to placebo (Table B-III), except for children receiving the first dose of RV1 at 10 weeks or RV5 at ages 8, 9, and 10 weeks, in whom vaccine efficacy was not significant. However, no tendency was seen in the data and it is likely this was due to the small size of the pooled studies.

The current evidence is weak, based on direct comparison of two small RV1 RCTs not powered to observe an effect on mortality, and on stratification of RCTs not designed to measure a difference between different vaccine schedules.

B.1.4. Severe rotavirus gastroenteritis after rotavirus vaccine administration while given simultaneously with other childhood vaccines

No clinical data from RCTs or from observational studies of RV1 and RV5 vaccines are available directly comparing details of simultaneous vaccination with other childhood vaccines. Indirect comparisons from stratification of RV1 and RV5 RCTs grouped as to whether there was no restriction on childhood vaccinations given, only oral polio vaccine (OPV) was not allowed, or none of the other childhood vaccines were given simultaneously, did not show a significant impact on rotavirus vaccine efficacy against severe rotavirus gastroenteritis compared to placebo, except for one trial of RV5 (*Finland and USA RV5*, stratum A) in which OPV was not allowed within two weeks of RV5 vaccination (Table B-III). The current evidence however is very weak, based only on stratification of RCTs not designed to measure a difference between different vaccine schedules. vaccines efficacy against severe rotavirus gastroenteritis compared to placebo, except for pooled data from two RV1 RCTs showing a better efficacy for vaccine compared to placebo when OPV were not allowed. No pattern was seen in the data and this finding might be due to chance only.

B.2. Policy implications of these findings

There is some evidence from RCTs that rotavirus vaccines may perform differently in countries from strata D and E compared to countries on strata A and B, although this information is limited by the fact that the four largest multi-center RCTs were added to more than one strata and three RCTs provided data only for a subset of the children randomised during the second year follow up. Evidence from case-control and historical control studies showed that RV1 and RV5 vaccines appear to be more effective for children receiving full schedule (two doses of RV1 or three doses of RV5) when compared to those receiving partial number of doses. There is also not enough evidence to justify extending the age range, changes on interval between doses or adding a third dose to the current RV1 schedule.

Post-implementation surveillance studies exploring the use of RV1 and RV5 for older children, longer interval between doses, different intervals between doses, or concomitant use of different vaccines would contribute to our knowledge and help support policy decisions. In addition, there is a need for RCTs from countries from strata D and E to be designed specifically to measure a difference between different vaccine schedules, in particular whether adding a third dose of RV1 would have any impact on vaccine efficacy.

2. AVAILABLE EVIDENCE ON THE SAFETY OF VARIOUS ROTAVIRUS VACCINE SCHEDULES

SERIOUS ADVERSE EVENTS (SAE) AFTER ROTAVIRUS VACCINE ADMINISTRATION

Data from RCTS of RV1 and RV5 show they do not increase the risk of severe adverse events in different WHO mortality strata.

Overall effect:

- Twenty-five RCTs of RV1 and six RCTs of RV5 were performed in strata A, B, D, and E. Serious adverse events were actively sought for up to 42 days after the children received vaccine or placebo, and passively collected until the end of trial's follow up.
- For RV1, two small safety trials reported no serious adverse events; pooled data for each strata showed that children receiving placebo tended to report more serious adverse events than children receiving vaccine, these results were marginally significant. For RV5, there was no statistically significant difference between children receiving vaccine or placebo regarding the number of serious adverse events. A passive surveillance study from Mexico reported an overall risk of 2.9 serious adverse events by 1,000,000 administered doses of RV1.

Number of doses:

- One RCT reported serious adverse events after 6 months of follow up comparing three and two doses of RV1 given in a 6-10-14 weeks schedule. There was no statistically significant difference in the number of serious adverse events between children receiving three or two doses of RV1.

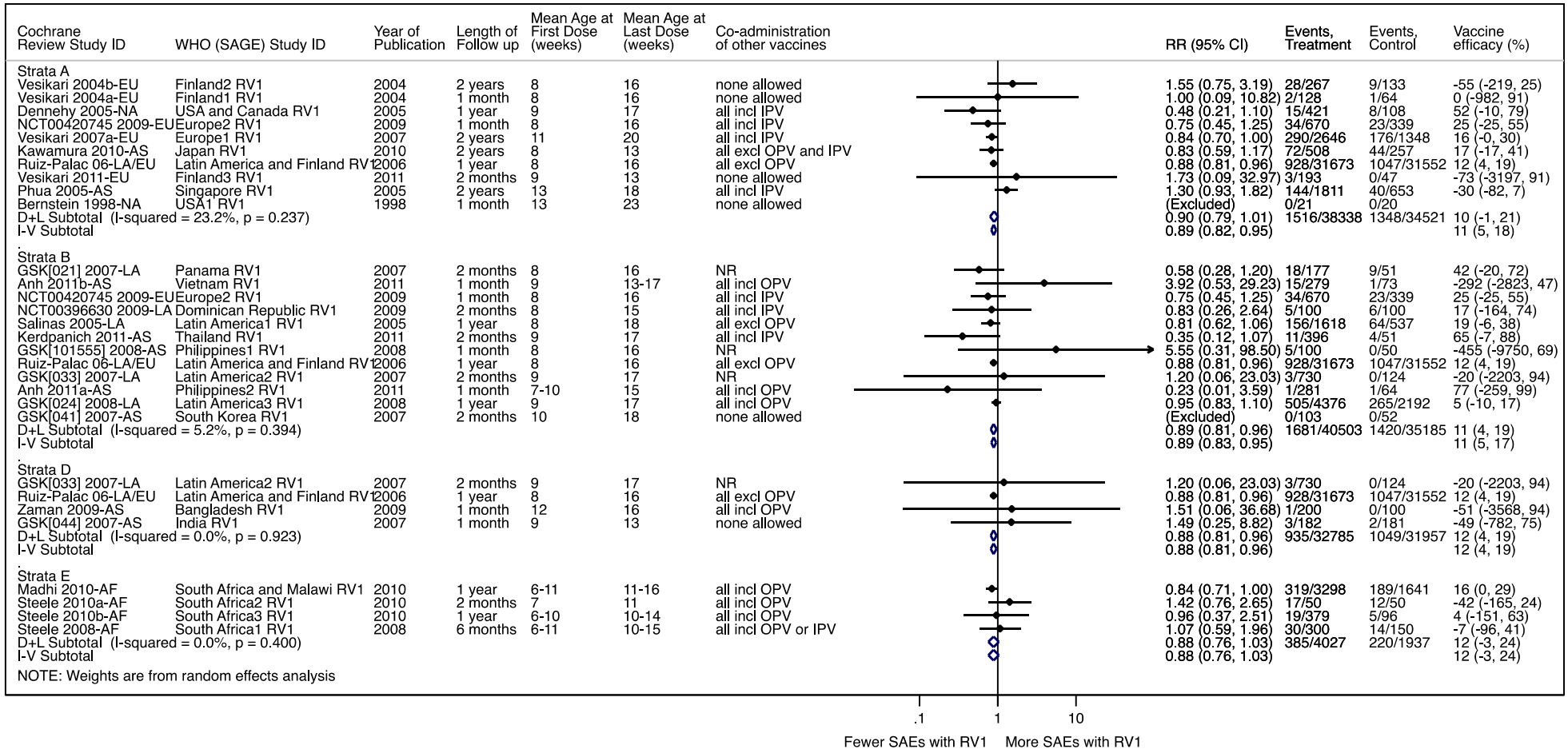
Age at first dose and last dose:

- One RCT reported serious adverse events after 6 months of follow up comparing children receiving the first dose of RV1 at 6 vs. 10 weeks of age. RV1 and placebo were given in a 6-10-14 weeks schedule. There was no statistically significant difference in the number of serious adverse events between children receiving the first dose of vaccine at age 6 or 10 weeks. Indirect comparisons from stratification of RV1 and RV5 RCTs using different mean ages of children receiving the first or last dose of RV1 or RV5 have not shown any significant difference in the reported number of serious adverse events in children receiving vaccine or placebo.

Concomitant use of other childhood vaccines:

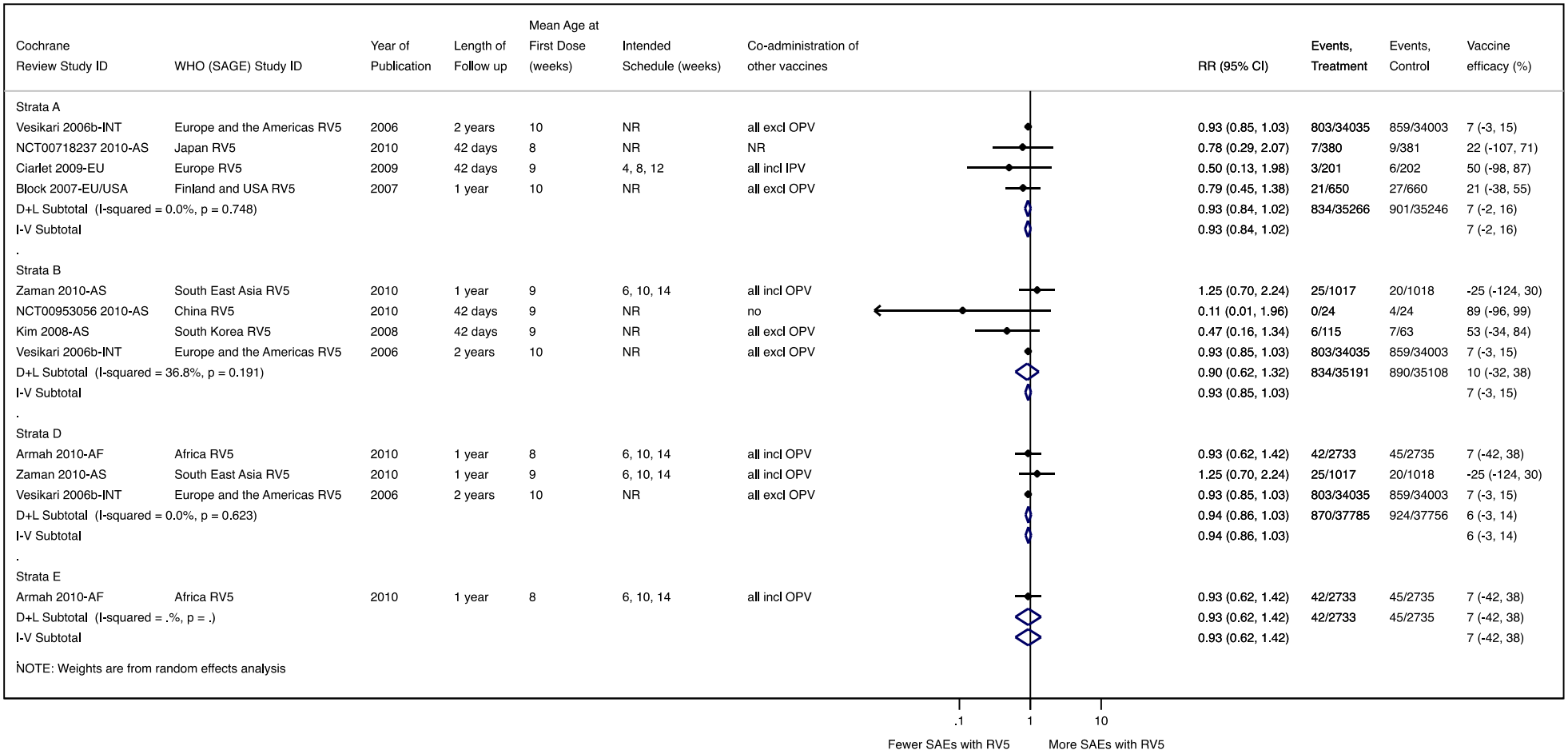
- One RV1 and one RV5 RCTs directly compared rotavirus vaccines with or without OPV and showed no statistically significant difference in the number of serious adverse events. Another RV5 RCT compared he use of RV5 with meningococcal vaccine or meningococcal vaccine alone, and also reported no statistical significant difference. Indirect comparisons from stratification of RV1 and RV5 RCTs reporting different vaccine schedules regarding concomitant administration of other vaccines have not shown any significant difference in the reported number serious adverse events in children receiving vaccine or placebo.

FIGURE VIII: RCTS OF RV1 VS. PLACEBO – SERIOUS ADVERSE EVENTS AFTER ROTAVIRUS VACCINATION STRATIFIED ACCORDING TO WHO MORTALITY STRATA



Legend Figure VIII:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Studies stratified according to the World Health Organization list of member states by mortality stratum (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). Three multi-centric trials were performed in more than one region and contributed to more than one stratum.(2, 3, 61) All children in *South Africa2 RV1*(4) and part of children in *South Africa and Malawi RV1*(5) were HIV positive. Horizontal axis represents effect estimate comparing groups of children receiving RV1 vs. placebo; vertical line through 1 shows no difference in serious adverse events between groups; effect estimate might differ between studies depending on data provided in trial reports. Black diamonds represent point estimate of risk ratio combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of RV1 (fewerSAEs with RV1), points to the right of the line show a detrimental effect of RV1 (more SAEs with RV1); I^2 value is the level of statistical heterogeneity between trials.CI=confidence interval; NR=not reported; OPV=oral polio vaccine; RR=risk ratio

FIGURE IX: RCTS OF RV5 VS. PLACEBO – SERIOUS ADVERSE EVENTS AFTER ROTAVIRUS VACCINATION STRATIFIED ACCORDING TO WHO MORTALITY STRATA



Legend Figure IX:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Studies stratified according to the World Health Organization list of member states by mortality stratum (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). Three multi-center RCTs were performed in more than one region and contributed to more than one stratum.(6, 7, 29) Horizontal axis represents effect estimate comparing groups of children receiving RV5 vs. placebo; vertical line through 1 shows no difference in serious adverse events between groups; effect estimate might differ between studies depending on data provided in trial report. Black diamonds represent point estimate of risk ratio combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of RV5 (fewer SAEs with RV5), points to the right of the line show a detrimental effect of RV5 (more SAEs with RV5); I^2 value is the level of statistical heterogeneity between trials. CI=confidence interval; IPV=inactivated polio vaccine; NR=not reported; OPV=oral polio vaccine; RR=risk ratio

C.1. Summary of results

C.1.1. SAE after rotavirus vaccine administration according to WHO mortality strata

Twenty-five RCTs of RV1(2-5, 8, 10-16, 18-21, 23-25, 29, 37, 61-64) and six of RV5(6, 7, 26, 28, 29, 65-67)were performed in strata A, B, D, and E. Serious adverse events were actively sought for up to 42 days after the children received vaccine or placebo, and passively collected until the end of trial's follow up. For RV1, two small safety trials reported no serious adverse events(13, 62); pooled data for each strata showed that children receiving placebo tended to report more serious adverse events than children receiving vaccine, these results were marginally significant (Figure VIII). For RV5, there was no statistically significant difference between children receiving vaccine or placebo regarding the number of serious adverse events (Figure IX). A recently published passive surveillance study from Mexico reported that after 7,691,757 doses of RV1 vaccine were administered during 2008-2009, 82 children reported a serious adverse event deemed to be associated with the vaccine, giving an overall risk of 2.9 events by 1,000,000 administered doses.(68)

There is strong evidence from RCTs that both RV1 and RV5 vaccines are not associated with more cases of serious adverse events, regardless of country's strata.

C.1.2. SAE after rotavirus vaccine administration by number of doses given

A single RCT (South Africa3 RV1(21)), reported serious adverse events after 6 months of follow up comparing three and two doses of RV1. This RCT was designed to measure vaccine immunogenicity; RV1 and placebo were given in a 6-10-14 weeks schedule, and all other vaccines were allowed concomitantly with RV1 (Table C-I). In this RCT nine of the children receiving three doses of RV1 and ten children receiving two doses of RV1 had a serious adverse event (RR 0.90, 95%CI 0.38-2.18, N=379). No clinical data from RCTs of RV5 vaccines or from observational studies of RV1 and RV5 vaccines are available directly comparing different number of doses and reporting serious adverse events. The current evidence is weak, based on a single small RCT of RV1 vaccine.

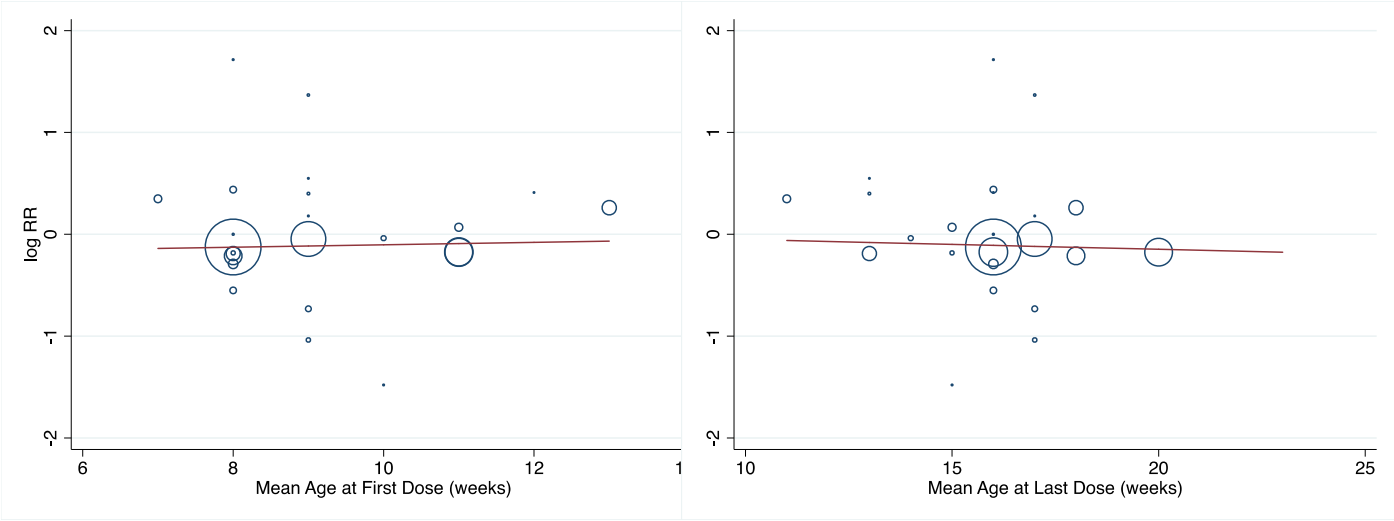
C.1.3. SAE after rotavirus vaccine administration by age at first and last dose

A single RCT (South Africa3 RV1(21)) reported serious adverse events after 6 months of follow up comparing children receiving the first dose of RV1 at 6 or 10 weeks of age. This RCT was designed to measure vaccine immunogenicity; RV1 and placebo were given in a 6-10-14 weeks schedule, and all other vaccines were allowed concomitantly with RV1 (Table C-II). In this RCT, nine of the children receiving the first dose of RV1 at age 6 weeks, and 10 of the children receiving the first dose of RV1 at age 10 weeks had a serious adverse event (RR 0.90, 95%CI 0.38-2.18, N=379).

In addition, indirect comparisons from stratification of RV1 and RV5 RCTs using different mean ages of children receiving the first or last dose of RV1 or RV5 did not show significant differences in the reported number of serious adverse events in children receiving vaccine or placebo (Table C-IV). Random-effect meta-regression using the mean age at first or last dose of RV1 vaccine reported an I^2 residual (proportion of residual variation due to heterogeneity) of 6.55% for mean age at first dose and of 6.88% for mean age at last dose and an adjusted R^2 (proportion of between-study variance explained) was of 0% for both mean ages, showing that in these RV1 RCTs, age at first dose or last dose did not influence vaccine efficacy (Figure X).

The current evidence is moderate, based on data from a single small study and mainly on stratification of RCTs not designed to measure a difference between different vaccine schedules.

FIGURE X: RCTS OF RV1 VS. PLACEBO – META-REGRESSION OF LOGARITHM OF THE RELATIVE RISK AGAINST THE MEAN AGE AT FIRST AND LAST VACCINE DOSE



Legend Figure X:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Meta-regression of 24 RCTs comparing RV1 vs. placebo. Vertical axis represents the logarithm of the relative risk of developing a serious adverse event comparing groups of children receiving RV1 vs. placebo; horizontal line shows the average age of children in each trial (weeks). I^2 residual (proportion of residual variation due to heterogeneity) was 6.55% for mean age at first dose and of 6.88% for mean age at last dose. Adjusted R^2 (proportion of between study variance explained) was of 0% for both mean ages.

C.1.4. SAE AFTER ROTAVIRUS VACCINE ADMINISTRATION WHILE GIVEN SIMULTANEOUSLY WITH OTHER CHILDHOOD VACCINES

One RV1 RCT directly compared receiving oral polio vaccine (OPV) simultaneously with rotavirus vaccine (Bangladesh RV1(25)) compared to RV1 alone, and reported no impact on serious adverse events, with one reported serious adverse event in the group of children randomized to RV1 and OPV and no serious adverse events in the group of children receiving RV1 only (Table C-III). All children in this study were vaccinated with Diphteria-Tetanus-acellular Pertussis and Hepatitis B vaccines.

Two RV5 RCTs directly compared children receiving RV5 simultaneously with OPV or meningococcal serogroup C conjugate vaccine (MenCC). *Latin America RV5*(34) compared children vaccinated with RV5 and OPV with children receiving RV5 without OPV, all children were also vaccinated with Diphteria-Tetanus-acellular Pertussis (DPT) and Hepatitis B vaccines. This RCT reported three serious adverse events among 372 children vaccinated with RV5 and OPV and five serious adverse events among 363 children vaccinated with RV5 without OPV (Table C-III). *Finland2 RV5*(69) compared children vaccinated with RV5 and MenCC with children receiving only MenCC, all children were also vaccinated with Diphteria-Tetanus-acellular Pertussis (DPT) and Hepatitis B vaccines. This RCT reported one serious adverse events among 116 children vaccinated with RV5 and MenCC and one serious adverse events among 122 children vaccinated with MenCC alone (Table C-III).

No clinical data from observational studies of RV1 or RV5 vaccines are available directly comparing rotavirus vaccines given alone or simultaneously with other childhood vaccines and reporting serious adverse events. Indirect comparisons from RV1 and RV5 RCTs stratified according to 1) no restriction on childhood vaccinations given, 2) only oral polio vaccine (OPV) was not allowed, or 3) none of the other childhood vaccines were given simultaneously did not shown a significant impact on the reported number of serious adverse events in children receiving vaccine or placebo (Table C-III). The current evidence however is very weak, based only on stratification of RCTs not design to measure a difference between different vaccine schedules.

C.2. POLICY IMPLICATIONS OF THESE FINDINGS

There is good evidence from RCTs that children receiving rotavirus vaccines are not at increased risk of serious adverse events when compared to children receiving placebo. In fact, children receiving RV1 reported significantly less serious adverse events when compared to placebo, with no statistically significant difference between vaccine and placebo and seen with RV5. Limited evidence from a single small study showed no significant difference on the number of serious adverse events for children receiving three or two doses of RV1, and for children starting vaccination at 6 or 10 weeks of age. Limited evidence from stratification of RCTs according to schedule details also showed no increased risk of serious

adverse events for different mean ages of first and last dose, and for RV1/RV5 simultaneously administered with other childhood vaccines.

Post-implementation monitoring of serious adverse events with RV1 and RV5 should continue and results reported in different parts of the world.

RISK OF INTUSSUSCEPTION (IS) AFTER ROTAVIRUS VACCINE ADMINISTRATION

Limited evidence from RCTS of RV1 and RV5 showed no increase in the risk of intussusception in different WHO mortality strata. RCTs also have not shown a statistically significant association between rotavirus vaccine and intussusception cases 1-7 or 1-42 days after each dose of the vaccine. Weak evidence from a case control study showed an excess of cases of intussusception after first and second dose in Mexico, second dose in Brazil with RV1 in Brazil. RV5 was also associated with an excess of cases of intussusception after second dose in Australia.

Overall effect:

- Eleven RCTs of RV1 and six of RV5 were performed in strata A, B, D, and E. Data on intussusception was actively sought for collection until the end of trial's follow up and in most cases confirmed using the Brighton Collaboration definition.
- Overall data from RCTs did not shown a statistically significant difference in the rate of intussusception for children receiving RV1 or RV5 vs. placebo. Four RCTS also provided the number of intussusception cases occurring 1-7 days or 1-42 days after each vaccine dose, and a statistically significant difference was also not showed between children receiving vaccines or placebo.
- Thirteen observational studies reporting on specific surveillance for intussusception in Australia, Brazil, France, Germany, Mexico, Singapore, and USA. Most of these studies did not provide risk estimation or compared the results with unvaccinated children. Results from a case-control study reported an increased risk after RV1 doses one and two in Mexico and after the second dose of RV1 in Brazil up to 14 days after vaccination, and a surveillance study from Australia an increased risk after the first RV5 dose in children aged one to three months up to seven days and up to 21 days after vaccination.

Number of doses:

- No clinical data from RCTs or from observational studies of RV1 and RV5 vaccines are available directly comparing RV1 or RV5 vaccines given different number of doses and reporting intussusception.

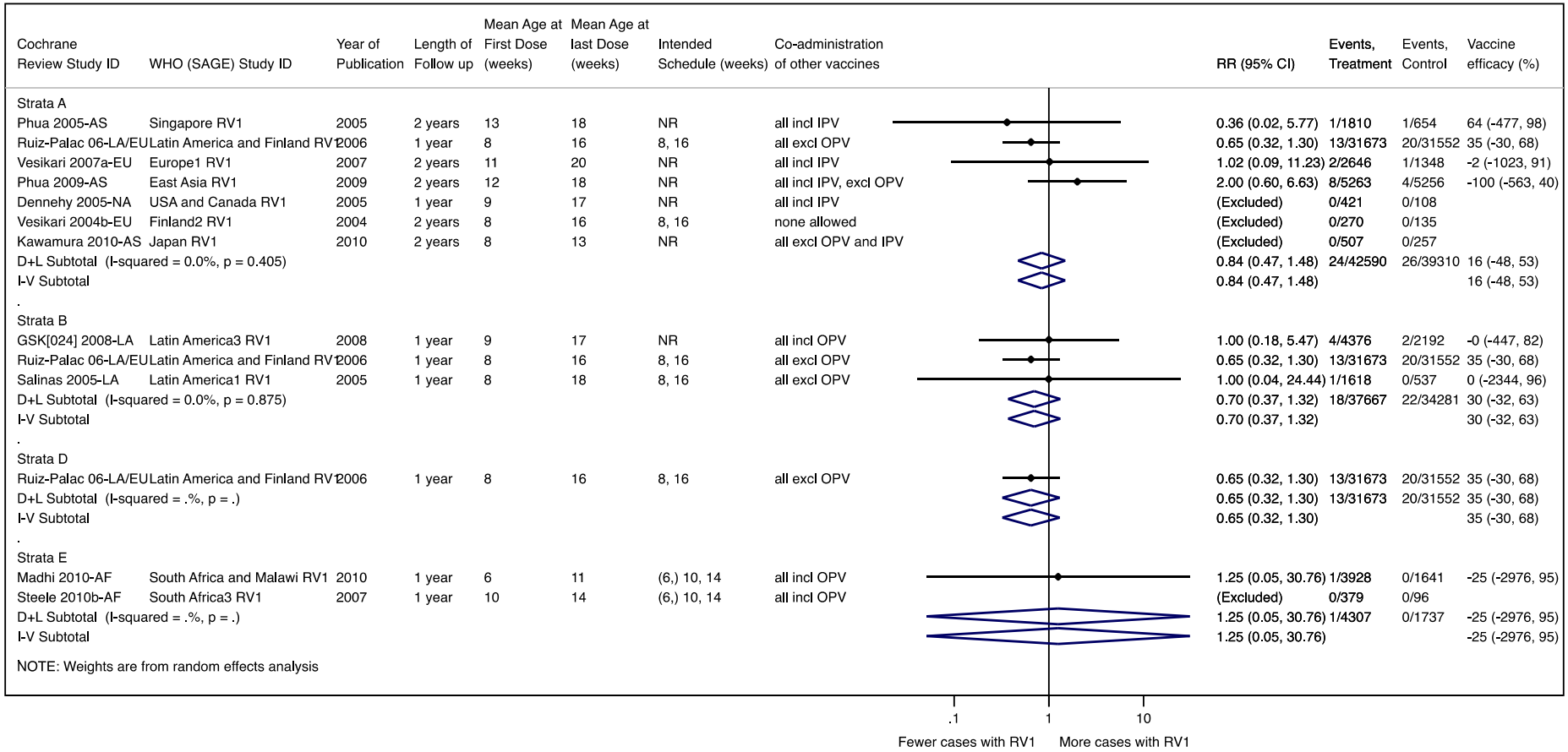
Age at first dose and last dose:

- No clinical data from RCTs or from observational studies of RV1 and RV5 vaccines are available directly comparing RV1 or RV5 vaccines with different ages of first or last doses of vaccines. Indirect comparisons from stratification of RV1 and RV5 RCTs using different mean ages of children receiving the first or last dose of RV1 or RV5 have not shown any significant difference in the reported number of serious adverse events in children receiving vaccine or placebo.

Concomitant use of other childhood vaccines:

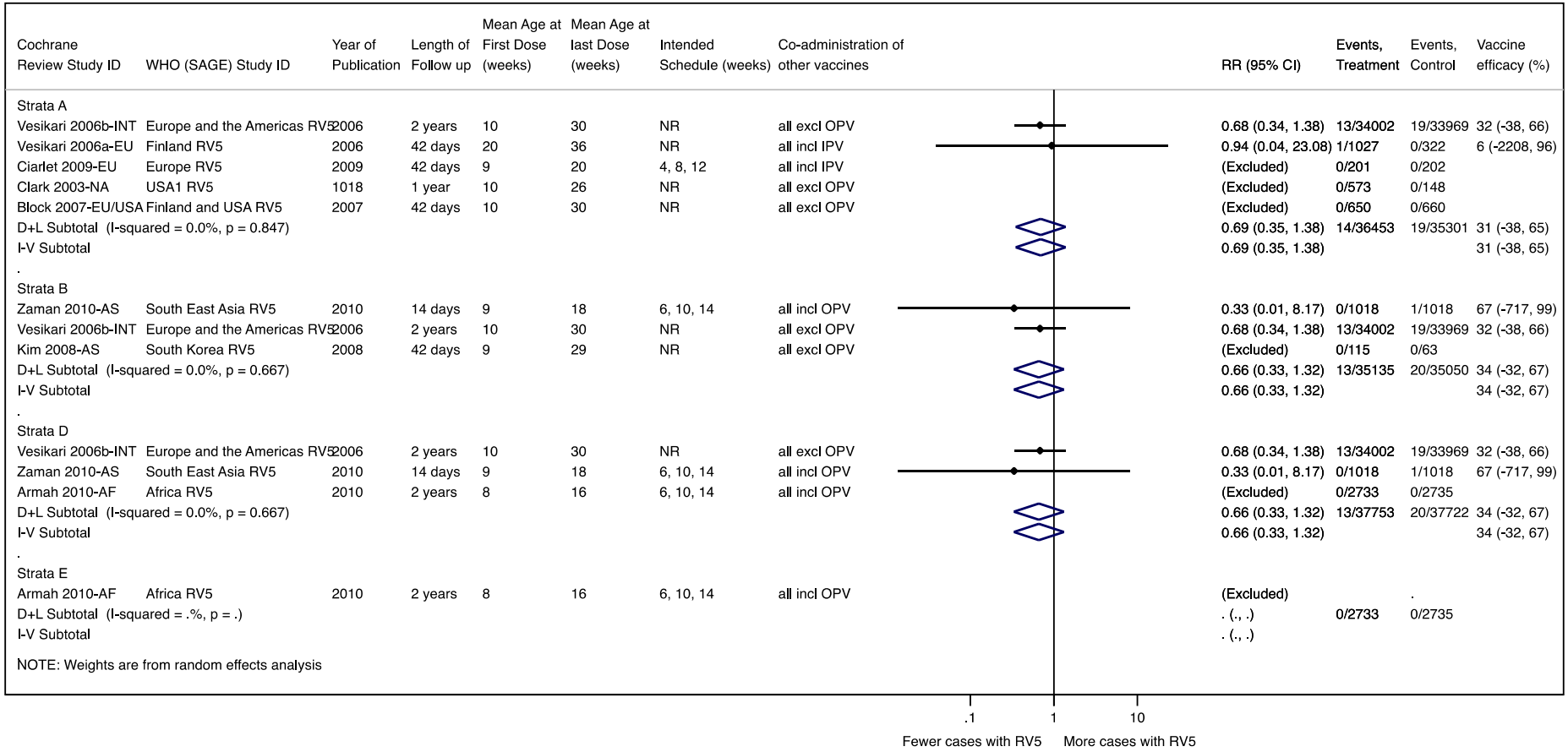
- One small RCT comparing RV5+OPV with RV5 alone reported a single case of intussusception 3 days after the third dose of RV5 alone. Indirect comparisons from stratification of RV1 and RV5 RCTs reporting different vaccine schedules regarding concomitant administration of other childhood vaccines have not shown any significant difference in the reported number intussusception in children receiving vaccine or placebo.

FIGURE XI: RCTS OF RV1 VS. PLACEBO – CASES OF INTUSSUSCEPTION AFTER ROTAVIRUS VACCINATION STRATIFIED ACCORDING TO WHO MORTALITY STRATA



Legend Figure VIII:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Studies stratified according to the World Health Organization list of member states by mortality stratum (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). One multi-centric trial was performed in more than one region and contributed data on strata A, B, and D.(3) All children in *South Africa2 RV1*(4) and part of children in *South Africa and Malawi RV1*(5) were HIV positive. Horizontal axis represents effect estimate comparing groups of children receiving RV1 vs. placebo; vertical line through 1 shows no difference in intussusception between groups; effect estimate might differ between studies depending on data provided in trial report. Black diamonds represent point estimate of risk ratio combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of RV1 (fewer cases with RV1), points to the right of the line show a detrimental effect of RV1 (more cases with RV1); I^2 value is the level of statistical heterogeneity between trials. CI=confidence interval; NR=not reported; OPV=oral polio vaccine; RR=risk ratio

FIGURE XII: RCTS OF RV5 VS. PLACEBO – CASES OF INTUSSUSCEPTION AFTER ROTAVIRUS VACCINATION STRATIFIED ACCORDING TO WHO MORTALITY STRATA



Legend Figure IX:
Data extracted from Soares-Weiser et al (2012) Cochrane review.(1) Studies stratified according to the World Health Organization list of member states by mortality stratum (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). Three multi-centric trials were performed in more than one region and contributed to more than one stratum.(6, 7, 29) Horizontal axis represents effect estimate comparing groups of children receiving RV5 vs. placebo; vertical line through 1 shows no difference in intussuception between groups; effect estimate might differ between studies depending on data provided in trial report. Black diamonds represent point estimate of risk ratio combined using the inverse of variance random effects meta-analysis; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of RV5 (fewer cases with RV5), points to the right of the line show a detrimental effect of RV5 (more cases with RV5); I^2 value is the level of statistical heterogeneity between trials. CI=confidence interval; IPV=inactivated polio vaccine; NR=not reported; OPV=oral polio vaccine; RR=risk ratio

D.1. SUMMARY OF RESULTS

D.1.1. RISK OF IS AFTER ROTAVIRUS VACCINE ADMINISTRATION ACCORDING TO WHO MORTALITY STRATA

Overall data on intussusception during the entire follow up period was provided for eleven RCTs of RV1(3, 5, 11, 15, 17-19, 21-23, 63) and nine of RV5(6, 7, 26-29, 34, 65, 70). RCTs were performed in strata A, B, D, and E, although none of them were powered to identify such a rare adverse event like intussusception. Nevertheless, intussusception cases were actively sought for the whole duration of the RCTs and for most trials confirmed by surgery, autopsy or imaging using the Brighton Collaboration case definition (www.brightoncollaboration.org).

For RV1, four of the eleven RCTs did not report any case of intussusception during the follow up period(15, 21, 22, 63); pooled overall data for each stratum is showed in Figure XI and did not report any significant difference in the rate of intussusception for children receiving RV1 or placebo. For RV5 also, five RCTs reported no events(26, 28, 29, 65, 70), and there was no statistically significant difference on the pooled number of cases of intussusception for children receiving RV5 vaccine or placebo (Figure XII).

Only five of the included RCTs provided information on the number of cases of intussusception occurring after each administered dose of RV1 or RV5 vaccines.

Latin America and Finland RV1(3) randomized 31,673 children to RV1 and 31,552 to placebo. Two cases each of intussusception with RV1 and with placebo were reported up to seven days after vaccination after the second vaccine dose. Intussusception cases up to 42 days after administration were one case after RV1 and 2 cases after placebo after the first dose, and 6 cases each after the second dose(71). A second RV1 RCT, *Singapore RV1* (18), reported a single case of intussusception that occurred during the first 7 days after RV1 vaccination and no cases on children receiving placebo. None of the results from RV1 RCTs were statistically significant (see Table D-I).

Europe and the Americas RV5(7) was also a large RCT in which 34,821 children were randomized to receive RV5 and 34,768 to placebo. In the RV5 group, up to 7 days after first dose no cases of intussusception was reported, one case was reported after the second dose of RV5, and no cases reported after the third dose. Up to 42 days after the first dose one case was reported with placebo, after the second dose, four cases were reported with RV5 and one case with placebo, and after the third dose two cases with RV5 and one with placebo(72). *Finland RV5*(27) reported a single case of intussusception that occurred in one of 1027 children randomized to RV5 between 7 and 42 days; and *Latin America RV5*(34) reported a single case of intussusception that occurred in one of 363 children randomized to RV5 alone between 0-7 days. None of the results from RV5 RCTs were statistically significant (Table D-I).

Following RV1 vaccination, one case-control study (*Brazil and Mexico RV1*(73)) reported vaccine to be associated with an increased risk of intussusception 1-7 days after first dose (out of 274 cases 24 were vaccinated, and out of 701 controls 17 were vaccinated; OR 5.8, 95% CI 2.6-13.0), and 8-14 days after the second dose (19 out of 254 cases 1 were vaccinated, and 24 out of 679 controls were vaccinated; OR 2.3, 95% CI 1.2-4.4) in Mexico. *Brazil and Mexico RV1* also reported RV1 to be associated with an increased risk of intussusception 1-7 days after second in dose in Brazil (21 out of 300 cases were vaccinated, and 50 out of 1169 controls were vaccinated; OR 1.9, 95% CI 1.1-3.4). A surveillance study (*Australia3 RV1-RV5* (74)) reported a non-significant excess of observed cases compared to expected cases of intussusception in children 1 to 3 months of age, 1-7 days and 1-21 days after the first dose in Australia (Table D-I).

In addition, anecdotal reports of intussusception were provided in three studies: a case-series study(75) of spontaneously reported cases of intussusception worldwide comparing incidence ratios after the first and second doses reported that the incidence ratio 3-7 days after the first dose was five times as high as that for the same period after the second dose. Two additional surveillance studies(76, 77) reported information only in an abstract and reported no statistically significant association between RV1 and intussusception in Mexico(76) and Singapore.(77) In addition, a recently published surveillance study from Mexico (Mexico3 RV1(68) reported one case of intussusception after the first RV1 dose and 3 cases after the second dose, after 7,691,757 doses have been administered. Details of each included observational study are presented in Table A4.5a and in Appendix 4.

For RV5, *Australia3 RV1-RV5*(74) reported a statistically significant excess of observed cases compared to expected cases in children aged 1 to 3 months of age, 1-7 days (RR 5.26, 95% CI 1.09-15.4; 3 events in 111533 vaccinated children) and 1-21 days (RR 3.51, 95% CI 1.29-7.64; 6 events in 111533 vaccinated children) after the first dose. Two surveillance studies in the USA (*USA3 RV5* (78, 79); USA13 RV5(80, 81) reported an excess of observed compared to expected cases of intussusception, but no statistical significance was found. Another study (France RV5(40)) reported a series of cases of

intussusception after RV5 vaccination without comparing to any baseline data. Data are presented in detail in Table A4.5b and Appendix 4.

The current evidence is weak, based on direct comparison of RV1 and RV5 RCTs that were not powered to identify rare events such as cases of intussusception, and a few surveillance studies performed mainly in countries on strata A and B.

D.1.2. Risk of IS after rotavirus vaccine administration according to number of doses given

No clinical data from RCTs or from observational studies of RV1 and RV5 vaccines are available directly comparing RV1 or RV5 vaccines given different number of doses and reporting intussusception.

D.1.3. Risk of IS after rotavirus vaccine administration by age at first dose and by interval between doses

No clinical data from RCTs or from observational studies of RV1 and RV5 vaccines are available directly comparing RV1 or RV5 vaccine schedules and reporting intussusception. Indirect comparisons from stratification of RV1 and RV5 RCTs using different mean ages of children receiving the first or last dose of RV1 or RV5 have not shown any significant difference in the reported number of intussusception in children receiving vaccine or placebo (Table D-II).

D.1.4. Risk of IS after rotavirus vaccine administration given simultaneoulsy with other vaccines

One RV5, *Latin America RV5*(34) compared children vaccinated with RV5 and OPV with children receiving RV5 without OPV, all children were also vaccinated with Diphteria-Tetanus-acellular Pertussis (DPT) and Hepatitis B vaccines. This RCT reported no cases of intussusception events among 372 children vaccinated with RV5 and OPV and one case among 363 children vaccinated with RV5 without OPV (Table D-I).

No clinical data from RCTs of RV1 vaccine or from observational studies of RV1 and RV5 vaccines are available directly comparing RV1 or RV5 vaccines given simultaneously with other childhood vaccines and reporting intussusception. Indirect comparisons from stratification of RV1 and RV5 RCTs grouped as to whether there was 1) no restriction on childhood vaccinations given, 2) only oral polio vaccine (OPV) was not allowed, or 3) none of the other childhood vaccines were given simultaneously, did not show a significant impact on the reported number of cases of intussusception in children receiving vaccine or placebo (Table D-II). The current evidence however is very weak, based only on stratification of RCTs not designed to measure a difference between different vaccine schedules.

D.2. Policy implications of these findings

Currently, there is very limited evidence from RCTs, surveillance and case-control studies on whether children receiving rotavirus vaccines are at increased risk of intussusception. There is even less evidence regarding risk of IS after each vaccine dose. Randomized trials evaluating RV1 and RV5 were not primarily designed to evaluate rare adverse events, such as intussuception, as a result, most trials lack precision to examine the impact of RV1 and RV5 on intussusception with different schedules.

In the included RCTs children receiving RV1 and RV5 did not report more cases of intussusception when compared to placebo. Limited evidence from a case-control study in Brazil and Mexico reported RV5 to be associated with a small increase on the risk of intussusception. Limited evidence from a surveillance study in Australia also reported an association between RV5 and intussusception. Very limited evidence from stratification of RCTs according to schedule details showed no increased risk of intussusception for different mean ages of first and last dose, and for concomitant administration of RV1/RV5 with other childhood vaccines.

Post-implementation monitoring of intussusception with RV1 and RV5 should continue and results reported in different parts of the world.

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TABLES

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

REPORT TO WHO/IVR

KARLA SOARES-WEISER (MD, PHD)

ENHANCE REVIEWS LTD

February 2012
World Health Organization
Rotavirus report

LIST OF TABLES

A. IMPACT OF CURRENT ROTAVIRUS VACCINE IMMUNIZATION SCHEDULES COMPARED TO ALTERNATIVE SCHEDULES ON RELEVANT OUTCOMES: MORTALITY DATA TABLES

TABLE A-I: EFFECT OF DIFFERENT NUMBER OF DOSES OF ROTAVIRUS VACCINES ON ALL-CAUSE MORTALITY (WITHIN STUDY SCHEDULE COMPARISONS)

Schedule evaluated											
Doses	**Type of study**	**Number of studies**	**WHO Mortality stratum**	**Country and vaccine**	**Type of estimate**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**n/N 2 doses**	**n/N 3 doses**	**Heterogeneity test (I^2)**
2p vs. 3p	RCT	1	E	South Africa3 RV1*	RR	1.99	0.18	21.76	2/190	1/189	-

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio

TABLE A-II: EFFECT OF AGE AT 1ST DOSE OF ROTAVIRUS VACCINES ON ALL-CAUSE MORTALITY (WITHIN STUDY SCHEDULE COMPARISONS)

Age at 1st dose: mean age in weeks											
Mean age	**Type of study**	**Number of studies**	**WHO Mortality stratum**	**Country and vaccine**	**Type of estimate**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**n/N younger age**	**n/N older age**	**Heterogeneity test (I^2)**
6-7 wks vs. 10-11 wks	RCT	3	B, E	Philippines2 RV1†, South Africa1 RV1‡, South Africa3 RV1	RR	2.82	0.56	14.04	6/513	1/447	0

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio

* South Africa3 RV1 had two vaccine arms, 2 doses starting at 10 weeks and 3 doses starting at 6 weeks, and a placebo arm.

† Philippines2 RV1 had two vaccine arms, one with an interval of 4 weeks starting vaccination at 10 weeks and one with an interval of 8 weeks starting vaccination at 7 weeks, and a placebo arm.

‡ South Africa1 RV1 had two cohorts with two vaccine arms (RV1+OPV and RV1+IPV) and one placebo arm each, the first cohort starting vaccination at 6 weeks and the second cohort starting at 11 weeks. Other childhood vaccines that were co-administered were DTPa and HBV.

TABLE A-III: EFFECT OF INTERVAL BETWEEN DOSES OF ROTAVIRUS VACCINES ON ALL-CAUSE MORTALITY (WITHIN STUDY SCHEDULE COMPARISONS)

Interval between doses in weeks											
Interval	**Type of study**	**Number of studies**	**WHO Mortality stratum**	**Country and vaccine**	**Type of estimate**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**n/N 4 wk interval**	**n/N 8 wk interval**	**Heterogeneity test (I^2)**
4 wks vs. 8 wks	RCT	2	B	Philippines2 RV1, Vietnam RV1§	RR	2.94	0.12	71.49	1/284	0/276	0

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio

§ Vietnam RV1 had two vaccine arms, one with an interval of 4 weeks and one of 8 weeks, and a placebo arm.

TABLE A-IV: EFFECT OF CONCOMITANT ADMINISTRATION OF OTHER CHILDHOOD VACCINES WITH ROTAVIRUS VACCINES ON ALL-CAUSE MORTALITY (WITHIN STUDY SCHEDULE COMPARISONS)

Concomitant administered with other childhood vaccine											
Other vaccine	**Type of study**	**Number of studies**	**WHO Mortality stratum**	**Country and vaccine**	**Type of estimate**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**n/N RV1 with OPV**	**n/N RV1 w/o OPV**	**Heterogeneity test (I^2)**
OPV+RV1 vs RV1	RCT	1	D	Bangladesh RV1** (also with BCG, DTPa and HBV)	RR	0.33	0.01	7.92	0/99	1/97	-
OPV+RV5 vs RV5	RCT	1	B, D	Latin America RV5 (no restriction to other childhood vaccines imposed)	RR	0.98	0.06	15.54	1/372	1/363	-
OPV+RV1 vs IPV+RV1	RCT	1	E	South Africa1 RV1 (also with DTPa and HBV)	RR	0.50	0.05	5.46	1/150	2/150	-

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. BCG=Bacille Calmette-Guerin vaccine; CI=confidence interval; DTPa=Diphteria-Tetanus-acellular Pertussis vaccine ; HBV=Hepatitis B vaccine ; IPV=Inactivated polio vaccine OPV=Oral polio vaccine ; RCT=randomised controlled trial; RR=risk ratio; w/o=without

TABLE A-V: STUDIES STRATIFIED ACCORDING TO DIFFERENT ROTAVIRUS VACCINE SCHEDULES AND EFFECT ON ALL-CAUSE MORTALITY

** Bangladesh RV1 had two vaccine arms, one administering RV1 with OPV and one without. Other childhood vaccines that were co-administered were BCG, DTPa and HBV.

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Heterogeneity test (I^2)
Vaccine schedule (weeks)											
4, 8, 12 wks	RCT	1	A	Europe RV5	-	-	-	-	0/201	0/202	-
6, 10 wks	RCT	1	E	South Africa1 (6w) RV1	RR	0.37	0.09	1.63	3/181	4/90	-
6, 10, 14 wks	RCT	2	E	South Africa3 (3p) RV1, South Africa and Malawi RV1††	RR	0.81	0.56	1.16	84/4117	43/1689	0
6, 10, 14 wks	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	0.92	0.68	1.24	79/3740	86/3742	0
8, 16 wks	RCT	5	A, B, D	Finland2 RV1, Latin America1 RV1, Latin America2 RV1, Latin America and Finland RV1, South Korea RV1	RR	1.27	0.86	1.88	61/34,391	44/32,398	
8, 16, 24 wks	RCT	1	B	Panama1 RV1	-	-	-	-	0/177	0/51	-
10, 14 wks	RCT	2	E	South Africa1 (11w) RV1, South Africa3 (2p) RV1,	RR	0.49	0.05	4.40	2/309	1/108	0

†† South Africa and Malawi RV1 had two vaccine arms, 2 doses starting at 11 weeks and 3 doses starting at 6 weeks, and a placebo arm. However, for mortality, results were not reported split into these groups. Many of the participants were HIV positive.

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Heterogeneity test (I^2)
12, 16 wks	RCT	1	D	Bangladesh RV1	RR	1.51	0.06	36.68	1/200	0/100	-
Not reported	RCT	13	A, B, D, E	East Asia RV1, Europe1 RV1, Finland3 RV1, India RV1, Japan RV1, Latin America3 RV1, Philippines1 RV1, Philippines2 RV1, Singapore RV1, South Africa2 RV1[‡‡], Thailand RV1, USA2 RV1, Vietnam RV1	RR	0.96	0.48	1.93	22/16,133	14/10,279	0
Not reported	RCT	3	A, B, D	Europe and the Americas RV5, Finland1 RV5, Finland and USA RV5	RR	1.24	0.69	2.22	25/35,712	20/34,985	0
Not reported	Historical control study	1	B	Brazil RV1	The study reports a decline in all-cause mortality during the three years following initiation of RV1 in Brazil among children ≤ 1 year and no difference in children 2-4 years compared to unvaccinated children (adjusted data, years 2002-2005).						

[‡‡] South Africa2 RV1 administered 3 doses, all participants were HIV positive.

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Heterogeneity test (I^2)
Age at 1st dose: mean age in weeks											
6 weeks	RCT	2	E	South Africa1 (6wks) RV1, South Africa3 (3p) RV1	RR	0.42	0.11	1.62	4/370	4/138	0
7 weeks	RCT	1	E	South Africa2 RV1	RR	0.67	0.26	1.73	6/50	9/50	-
8 weeks	RCT	6	A, B, D	Finland2 RV1, Japan RV1, Latin America1 RV1, Latin America and Finland RV1, Panama1 RV1, Philippines1 RV1	RR	1.27	0.86	1.89	58/34,342	44/32,580	0
8 weeks	RCT	1	D, E	Africa RV5	RR	0.93	0.68	1.26	76/2723	82/2724	-
9 weeks	RCT	6	A, B, D	Finland3 RV1, India RV1, Latin America2 RV1, Latin America3 RV1, Thailand RV1, Vietnam RV1	RR	2.15	0.56	8.28	13/6162	2/2646	0
9 weeks	RCT	2	A, B, D	Europe RV5, South East Asia RV5	RR	0.75	0.17	3.35	3/1218	4/1220	-
10 weeks	RCT	4	A, B, E	Europe1 RV1, Philippines2 RV1, South Africa3 (2p) RV1, South Korea	RR	0.96	0.11	8.58	3/3187	0/1495	0

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Heterogeneity test (I^2)
				RV1							
10 weeks	RCT	2	A, B, D	Europe and the Americas RV5, Finland and USA RV5	RR	1.24	0.69	2.22	25/34,685	20/34,663	0
11 weeks	RCT	2	E	South Africa1 (11wks) RV1, South Africa and Malawi RV1	RR	0.79	0.55	1.13	83/4047	44/1701	0
12 weeks	RCT	3	A, D	Bangladesh RV1, East Asia RV1, USA2 RV1	RR	0.84	0.17	4.16	3/5571	3/5463	0
13 weeks	RCT	1	A	Singapore RV1	RR	2.53	0.13	48.89	3/1779	0/642	-
20 weeks	RCT	1	A	Finland1 RV5[§§]	-	-	-	-	0/1027	0/322	-
Not reported	Historical control study	1	B	Brazil RV1	The study reports a decline in all-cause mortality during the three years following initiation of RV1 in Brazil among children ≤ 1 year and no difference in children 2-4 years compared to unvaccinated children (adjusted data, years 2002-2005).						

[§§] Finland1 RV5 started vaccination late, children 2-8 months were enrolled with a median age of 5 months at first vaccination dose. 3 doses were administered with an interval of 4-8 weeks.

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Heterogeneity test (I^2)
Interval between doses in weeks											
4 weeks	RCT	9	A, D, E	Bangladesh RV1, Finland3 RV1, Japan RV1, India RV1, Singapore RV1, South Africa1 RV1, South Africa2 RV1, South Africa3 RV1, South Africa and Malawi RV1	RR	0.77	0.56	1.06	99/7525	57/3167	0
4 weeks	RCT	3	A, B, D, E	Africa RV5, Europe RV5, South East Asia RV5	RR	0.92	0.68	1.24	79/3941	86/3944	0
4-8 weeks	RCT	6	A, B, D	East Asia RV1, Europe1 RV1, Latin America3 RV1, Latin America and Finland RV1, Philippines2 RV1, Vietnam RV1	RR	1.29	0.89	1.88	68/44,485	48/40,468	0
4-8 weeks	RCT	1	A	Finland1 RV5	-	-	-	-	0/1027	0/322	-
4-10 weeks	RCT	1	A, B, D	Europe and the Americas RV5	RR	1.20	0.66	2.17	24/34,035	20/34,003	-
4-11 weeks	RCT	1	A	Finland and USA RV5	RR	3.05	0.12	74.64	1/650	0/660	-

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Heterogeneity test (I^2)
6-10 weeks	RCT	1	A	USA2 RV1	RR	2.97	0.12	72.16	1/108	0/107	-
8 weeks	RCT	7	A, B, D	Finland2 RV1, Latin America1 RV1, Latin America2 RV1, Panama1 RV1, Philippines1 RV1(1), South Korea RV1, Thailand RV1	RR	0.84	0.13	5.40	5/3390	1/973	0
Not reported	Historical control study	1	B	Brazil RV1	The study reports a decline in all-cause mortality during the three years following initiation of RV1 in Brazil among children ≤ 1 year and no difference in children 2-4 years compared to unvaccinated children (adjusted data, years 2002-2005).						

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Heterogeneity test (I^2)
Co-administration of other vaccines											
Any other vaccine	RCT	11	A, B, D, E	Bangladesh RV1, Europe1 RV1, Latin America3 RV1, Philippines2 RV1, Singapore RV1, South Africa1 RV1, South Africa2 RV1, South Africa3 RV1, South Africa and Malawi RV1, Thailand RV1, Vietnam RV1	RR	0.81	0.59	1.10	110/ 14,580	59/6365	0
Any other vaccine including oral polio vaccine	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	0.92	0.68	1.24	79/3740	86/3742	0
Any other vaccine including inactivated polio vaccine	RCT	2	A	Europe RV5, Finland1 RV5	-	-	-	-	0/1228	0/524	-
Any other vaccine except oral polio	RCT	4	A, B, D	East Asia RV1, Japan RV1, Latin America1 RV1, Latin America and	RR	1.23	0.83	1.80	59/39,061	47/37,602	0

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Heterogeneity test (I^2)
vaccine				Finland RV1							
Any other vaccine except oral polio vaccine	RCT	2	A, B, D	Europe and the Americas RV5, Finland and USA RV5	RR	1.24	0.69	2.22	25/34,685	20/34,663	0
None allowed	RCT	5	A, B, D	Finland2 RV1, Finland3 RV1, India RV1, South Korea RV1, USA2 RV1	RR	2.97	0.12	72.16	1/860	0/523	0
Not reported	RCT	3	B, D	Latin America2 RV1, Panama1 RV1, Philippines2 RV1	RR	1.20	0.06	23.03	3/1007	0/225	-
Not reported	Historical control study	1	B	Brazil RV1	The study did not report data suitable for analysis, however, a decline in all-cause mortality during the three years following initiation of RV1 in Brazil among children ≤ 1 year and no difference in children 2-4 years compared to unvaccinated children (adjusted data, years 2002-2005) was reported. Country data were analysed with an interrupted time-series analysis that used diarrhoea-related mortality or hospitalization rates estimated for the years after rotavirus vaccination (2007–2009) compared with expected rates calculated from pre-vaccine years (2002–2005) adjusted for secular and seasonal trends. Rotavirus vaccination is administered with other vaccines on schedule and recommended at 2 and 4 months of age, with first dose administered at 6–14 weeks, and the second dose at 14–24 weeks of age.					

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio

TABLE A-VI: EFFECT OF ROTAVIRUS VACCINES ON DIARRHOEA RELATED MORTALITY*, WITHIN STUDY SCHEDULE COMPARISONS OR STRATIFICATION OF STUDIES**

Schedule detail	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	Pre-vaccine era	Post-vaccine era	Heterogeneity test (I^2)
Children ≤ 1 year Data for 2008 Not reported	Historical control studies	3	B	Brazil4 RV1†††	RRR	39	29	49	Vaccine coverage: 90% 1st dose, 77% 2nd dose		-
				Mexico1 RV1	RRR	41	36	47	Vaccine coverage: 74% 1st dose, 51% 2nd dose		-
				Panama2 RV1	RRR	45	40	51	Vaccine coverage: 91% 1st dose, 71% 2nd dose		-
Children 1-4 yrs Data for 2008 Not reported	Historical control studies	3	B	Brazil4 RV1	RRR	33	15	52	Vaccine coverage: 90% 1st dose, 77% 2nd dose		-
				Mexico1 RV1	RRR	24	14.25	33.53	Vaccine coverage: 74% 1st dose, 51% 2nd dose		-
				Panama2 RV1	RRR	54	48	60	Vaccine coverage: 91% 1st dose, 71% 2nd dose		-
Not reported	Historical control study	1	D	Nicaragua2 RV5	IRR	0.80	0.61	1.04	1.03/10,000 child-years	0.82/10,000 child-years	-

*** No RCTs and 6 observational studies reported diarrhoea related mortality; however, none of them gave details of number of doses, age at first dose, interval between doses or co-administration of other vaccines.

††† Data from companion paper Lanzieri et al 2011 was used for this outcome.

Not reported	Surveil-lance study and Cohort study	2	B, D	Latin America and the Caribbean RV1/RV5‡‡‡, Turkey RV1/RV5	For one study, 1 in 2874 children hospitalized for rotavirus infection died, but the impact of rotavirus vaccination on mortality was not investigated as only three of the participating countries had introduced vaccination during the study period. For the other study no children died, but no control group was reported.

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; IRR=incidence rate ratio; RRR=relative reduction in death rate

‡‡‡ These studies reported on both RV1 and RV5.

B. IMPACT OF ROTAVIRUS VACCINE IMMUNIZATION SCHEDULES ON SEVERE ROTAVIRUS GASTROENTERITIS

TABLE B-I: EFFECT OF DIFFERENT NUMBER OF DOSES OF ROTAVIRUS VACCINES ON SEVERE ROTAVIRUS GASTROENTERITIS (WITHIN STUDY SCHEDULE COMPARISONS)

Schedule evaluated[§§§]											
Doses	**Type of study**	**# of studies**	**WHO Mortality stratum**	**Country and vaccine**	**Type of estimate**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**n/N 2 doses**	**n/N 3 doses**	**Heterogeneity test (I^2)**
2p vs. 3p 1st year	RCT	2	E	South Africa3 RV1, South Africa and Malawi RV1	RR	0.78	0.21	2.90	31/1686	30/1687	45%
2p vs. 3p 2nd year	RCT	1	E	South Africa and Malawi RV1[****]	RR	4.58	0.99	21.05	9/418	2/425	-

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio

[§§§] All children receiving 3 doses of RV1 started the first dose at age 6 weeks, for those receiving 2 doses RV1 was started at 10-11 weeks of age. Latin America1 RV1 also compared 2 and 3 doses of RV1 vs. placebo, but have not provided data on severe RVGE.

[****] Only the cohort of Malawi was followed up in the second year of the study South Africa and Malawi RV1

TABLE B-II: EFFECT OF DIFFERENT NUMBER OF DOSES OF ROTAVIRUS VACCINES ON ROTAVIRUS DIARRHOEA RELATED HEALTH CARE ENCOUNTERS (PARTIAL VS. FULL SCHEDULE)

Doses	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N	Heterogeneity test (I^2)
1p vs. no vaccination	Case-control and Historical-control studies	4	A, B	El Salvador RV1, Australia1 RV1, Australia2 RV1, Brazil3 RV1	OR	0.61	0.36	1.06	-	5%
2p vs. no vaccination	Case-control and Historical-control studies	4	A, B	El Salvador RV1, Australia1 RV1, Australia2 RV1, Brazil3 RV1	OR	0.40	0.20	0.81	-	78%
1p vs. no vaccination	Case-control and Historical-control studies	7	A, D	Australia2 RV5, Nicaragua1 RV5, USA6 RV5, USA7 RV5, USA9 RV5, USA10 RV5, USA12 RV5	OR	0.34	0.20	0.59	-	69%
2p vs. no vaccination	Case-control and Historical-control studies	7	A, D	Australia2 RV5, Nicaragua1 RV5, USA6 RV5, USA7 RV5, USA9 RV5, USA11 RV5, USA12 RV5	OR	0.24	0.14	0.40	-	36%
3p vs. no vaccination	Case-control and Historical-control studies	8	A, D	Australia2 RV5, Nicaragua1 RV5, USA6 RV5, USA7 RV5, USA9 RV5, USA10 RV5, USA11 RV5, USA12 RV5	OR	0.18	0.11	0.29	-	63%

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; OR=odds ratio

TABLE B-III: STUDIES STRATIFIED ACCORDING TO DIFFERENT SCHEDULES AND EFFECT ON SEVERE ROTAVIRUS GASTROENTERITIS

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
Vaccine schedule (weeks)											
(6), 10, 14 wks 1st year	RCT	2	E	South Africa1 RV1, South Africa and Malawi RV1††††	RR	0.39	0.28	0.55	61/3353	73/1539	0
(6), 10, 14 wks 2nd year	RCT	1	E	South Africa and Malawi RV1	RR	0.41	0.19	0.91	11/843	13/408	-
6, 10, 14 wk 1st year	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	0.42	0.29	0.60	40/3348	96/3326	0
6, 10, 14 wk 2nd year	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	0.58	0.46	0.73	117/3348	200/3326	0
8, 16 wks 1st year	RCT	2	A, B, D	Latin America1 RV1, Latin America and Finland RV1	RR	0.21	0.12	0.34	39/10401	111/9312	42%
8, 16 wks 2nd year	RCT	2	A, B, D	Latin America1 RV1, Finland2	RR	0.17	0.06	0.48	5/577	13/232	0

†††† South Africa and Malawi RV1 had two vaccine arms, 2 doses starting at 11 weeks and 3 doses starting at 6 weeks, and a placebo arm. However, for mortality, results were not reported split into these groups. Many of the participants were HIV positive.

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
				RV1							
Not reported 1st year	RCT	3	A, B, D	Europe1 RV1, Latin America3 RV1, USA2 RV1	RR	0.11	0.04	0.33	14/6891	88/3508	69%
Not reported 2nd year	RCT	5	A, B, D	Europe1 RV1, East Asia RV1, USA2 RV1, Singapore RV1, Japan RV1	RR	0.10	0.07	0.14	31/10207	210/7617	0
Not reported 1st year	RCT	2	A	USA2 RV5, Finland and USA RV5	RR	0.07	0.01	0.51	0/738	14/747	0
Not reported 2nd year	RCT	2	A, B, D	Europe and the Americas RV5, Japan RV5	RR	0.09	0.03	0.34	2/1167	27/1110	0
Age at 1st dose: mean age in weeks											
8 weeks 1st year	RCT	2	A, B	Latin America1 RV1, Latin America and Finland RV1	RR	0.21	0.12	0.34	39/10401	111/9312	42%
8 weeks 2nd year	RCT	3	A, B, D	Finland2 RV1, Japan RV1, Latin America1 RV1	RR	0.14	0.06	0.32	7/1075	25/482	0
8 weeks	RCT	1	D, E	Africa RV5	RR	0.36	0.22	0.59	21/2357	58/2348	-

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
1st year											
8 weeks 2nd year	RCT	1	A, D, E	Africa RV5, Japan RV5‡‡‡‡	RR	0.26	0.02	2.73	79/2711	139/2702	68%
9 weeks 1st year	RCT	1	A, B, D	Latin America3 RV1	RR	0.18	0.08	0.44	7/4211	19/2099	-
9 weeks 1st year	RCT	2	A, B, D	Europe RV5, South East Asia RV5	RR	0.27	0.04	1.79	19/1178	46/1161	53%
9 weeks 2nd year	RCT	1	B, D	South East Asia RV5	RR	0.53	0.36	0.78	38/991	71/978	-
10 weeks 1st year	RCT	1	E	South Africa3 RV1[1]	RR	0.42	0.10	1.74	5/379	3/96	-
10 weeks 1st year	RCT	1	A	Finland and USA RV5	RR	0.08	0.00	1.39	0/551	6/564	-
10 weeks 2nd year	RCT	1	A, B, D	Europe and the Americas RV5	RR	0.11	0.03	0.47	2/813	17/756	-
11 weeks	RCT	2	A, E	South Africa and Malawi RV1,	RR	0.13	0.02	1.17	61/5546	130/2745	95%

‡‡‡‡ This study reported a mean age of 7.5 weeks.

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
1st year				Europe1 RV1							
11 weeks 2nd year	RCT	2	A, E	South Africa and Malawi RV1, Europe1 RV1	RR	0.19	0.05	0.77	35/3402	140/1770	89%
12 weeks 1st year	RCT	1	A	USA2 RV1	RR	0.22	0.05	1.00	2/108	9/107	-
12 weeks 2nd year	RCT	2	A	USA2 RV1, East Asia RV1	RR	0.08	0.02	0.32	5/5371	70/5363	54%
13 weeks 2nd year	RCT	1	A	Singapore RV1	RR	0.12	0.00	2.95	0/1779	1/642	-
Interval between doses in weeks											
4 weeks 1st year	RCT	2	E	South Africa3 RV1, South Africa and Malawi RV1	RR	0.39	0.28	0.55	61/3353	73/1539	0
4 weeks 2nd year	RCT	3	A, E	Singapore RV1, Japan RV1, South Africa and Malawi RV1	RR	0.21	0.06	0.68	13/3120	26/1300	46%
4 weeks 1st year	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	0.42	0.29	0.60	40/3348	96/3326	0

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
4 weeks 2nd year	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	0.58	0.46	0.73	117/3348	200/3326	0
4-8 weeks 1st year	RCT	3	A, B, D	Europe1 RV1, Latin America3 RV1, Latin America and Finland RV1	RR	0.11	0.05	0.25	24/15792	156/12259	70%
4-8 weeks 2nd year	RCT	2	A	East AsiaRV1, Europe1 RV1	RR	0.08	0.04	0.18	26/7822	178/6618	36%
4-11 weeks 1st year	RCT	1	A	Finland and USA RV5	RR	0.08	0.00	1.39	0/551	6/564	-
4-10 weeks 2nd year	RCT	2	A, B, D	Europe and the Americas RV5, Japan RV5	RR	0.09	0.03	0.34	2/1167	27/1110	0
6-10 weeks 1st year	RCT	1	A	USA2 RV1	RR	0.22	0.05	1.00	2/108	9/107	-
6-10 weeks 2nd year	RCT	1	A	USA2 RV1	RR	0.16	0.05	0.51	3/108	19/107	-
8 weeks 1st year	RCT	1	B, D	Latin America1 RV1	RR	0.26	0.16	0.42	27/1392	34/454	-

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
8 weeks 2nd year	RCT	2	A, B, D	Finland2 RV1, Latin America1 RV1	RR	0.17	0.06	0.48	5/577	13/232	0
8 weeks 1st year	RCT	1	A	USA2 RV5	RR	0.06	0.00	0.99	0/187	8/183	-

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
Co-administration of other vaccines											
Any other vaccine 1st year	RCT	3	B, D, E	Latin America3 RV1, South Africa3 RV1, South Africa and Malawi RV1	RR	0.33	0.21	0.52	68/7564	92/3638	21%
Any other vaccine 2nd year	RCT	1	E	South Africa and Malawi RV1	RR	0.41	0.19	0.91	11/843	13/408	-
Any other vaccine, including inactivated polio vaccine 1st year	RCT	1	A	Europe1 RV1	RR	0.04	0.02	0.10	5/2572	60/1302	-
Any other vaccine, including IPV 2nd year	RCT	2	A	Europe1 RV1, Singapore RV1	RR	0.10	0.07	0.15	24/4338	128/2004	0
Any other vaccine including oral polio vaccine 1st year	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	0.42	0.29	0.60	40/3348	96/3326	0

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
Any other vaccine including oral polio vaccine 2nd year	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	0.58	0.46	0.73	117/3348	200/3326	0
Any other vaccine except oral polio vaccine 1st year	RCT	2	A, B, D	Latin America1 RV1, Latin America and Finland RV1	RR	0.21	0.12	0.34	39/10401	111/9312	42%
Any other vaccine except oral polio vaccine 2nd year	RCT	3	A, B, D	Japan RV1, East Asia RV1, Latin America1 RV1	RR	0.08	0.03	0.20	6/6093	66/5615	10%
Any other vaccine except oral polio vaccine 1st year	RCT	1	A	Finland and USA RV5	RR	0.08	0.00	1.39	0/551	6/564	-
Any other vaccine except oral polio vaccine	RCT	1	A, B, D	Europe and the Americas RV5	RR	0.11	0.03	0.47	2/813	17/756	-

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
2nd year											
None allowed 1st year	RCT	1	A	USA2 RV1	RR	0.22	0.05	1.00	2/108	9/107	-
None allowed 2nd year	RCT	2	A	Finland2 RV1, USA2 RV1	RR	0.15	0.06	0.37	6/353	29/230	0
None allowed 1st year	RCT	1	A	USA2 RV5	RR	0.06	0.00	0.99	0/187	8/183	-
Not reported 2nd year	RCT	1	A	Japan RV5	RR	0.05	0.00	0.81	0/354	10/354	-

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio; OPV=oral polio vaccine; IPV=inactivated polio vaccine

C. EVIDENCE ON THE SAFETY OF VARIOUS ROTAVIRUS VACCINE SCHEDULES: RISK OF SERIOUS ADVERSE EVENTS AFTER ROTAVIRUS VACCINE ADMINISTRATION

TABLE C-I: EFFECT OF DIFFERENT NUMBER OF DOSES OF ROTAVIRUS VACCINES ON SERIOUS ADVERSE EVENTS (WITHIN STUDY SCHEDULE COMPARISONS)

Schedule evaluated											
Doses	**Type of study**	**Number of studies**	**WHO Mortality stratum**	**Country and vaccine**	**Type of estimate**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**n/N 3 doses**	**n/N 2 doses**	**Heterogeneity test (I^2)**
3p vs. 2p	RCT	1	E	South Africa3 RV1[§§§§]	RR	0.90	0.38	2.18	9/189	10/190	-

Blue colour=RV1; orange colour=RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio

TABLE C-II: EFFECT OF DIFFERENT MEAN AGE OF FIRST DOSE OF ROTAVIRUS VACCINES ON SERIOUS ADVERSE EVENTS (WITHIN STUDY SCHEDULE COMPARISONS)

Schedule evaluated											
Doses	**Type of study**	**Number of studies**	**WHO Mortality stratum**	**Country and vaccine**	**Type of estimate**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**n/N 3 doses**	**n/N 2 doses**	**Heterogeneity test (I^2)**
6w vs. 10w	RCT	1	E	South Africa3 RV1[*****]	RR	0.90	0.38	2.18	9/189	10/190	-

Blue colour=RV1; orange colour=RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio

[§§§§] South Africa3 RV1 had two vaccine arms, 2 doses starting at 10 weeks and 3 doses starting at 6 weeks, and a placebo arm.

[*****] South Africa3 RV1 had two vaccine arms, 2 doses starting at 10 weeks and 3 doses starting at 6 weeks, and a placebo arm.

TABLE C-III: EFFECT OF CONCOMITANT ADMINISTRATION OF OTHER CHILDHOOD VACCINES WITH ROTAVIRUS VACCINES ON SERIOUS ADVERSE EVENTS (WITHIN STUDY SCHEDULE COMPARISONS)

Concomitant administered with other childhood vaccine											
Other vaccine	**Type of study**	**Number of studies**	**WHO Mortality stratum**	**Country and vaccine**	**Type of estimate**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**n/N RV1 with OPV**	**n/N RV1 w/o OPV**	**Heterogeneity test (I^2)**
OPV+RV1 vs RV1	RCT	1	D	Bangladesh RV1†††††† (also with BCG, DTPa and HBV)	RR	0.32	0.01	7.92	0/99	1/97	-
OPV+RV5 vs RV5	RCT	1	B, D	Latin America RV5 (no restriction to other childhood vaccines imposed)	RR	0.59	0.14	2.43	3/372	5/363	-
RV5+MenCC vs MenCC	RCT	1	A	Finland2 RV5 (no restriction to other childhood vaccines imposed)	RR	1.05	0.07	16.62	1/116	1/122	

Blue colour=RV1; orange colour=RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio; OPV=oral polio vaccine; MenCC= meningococcal serogroup C conjugate vaccine

†††††† Bangladesh RV1 had two vaccine arms, one administering RV1 with OPV and one without. Other childhood vaccines that were co-administered were BCG, DTPa and HBV.

TABLE C-IV: EFFECT OF DIFFERENT VACCINATION SCHEDULES ON THE RISK OF SERIOUS ADVERSE EVENTS -- STUDIES STRATIFIED ACCORDING TO DIFFERENT SCHEDULES

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
Vaccine schedule (weeks)											
4, 8, 12 wks	RCT	1	A	Europe RV5	RR	0.50	0.13	1.98	3/201	6/202	-
(6), 10, 14 wks	RCT	2	E	South Africa and Malawi RV1, South Africa3 RV1	RR	0.84	0.71	1.00	338/3677	194/1737	0%
6, 10, 14 wks	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	1.03	0.73	1.45	67/3750	65/3753	0%
12, 16 wks	RCT	1	D	Bangladesh RV1	RR	1.51	0.06	36.66	1/200	0/100	-
6, 10/10, 14 wks	RCT	1	E	South Africa1 RV1	RR	1.07	0.59	1.96	30/300	141/150	-
8, 16 wks	RCT	7	A, B, D	Latin America2 RV1, Dominican Republic RV1, Finland2 RV1, Latin America and Finland RV1, Finland1 RV1, South Korea RV1	RR	0.88	0.81	0.96	1122/ 34619	1127/ 32562	0%
8, 16, 24	RCT	1	B	Panama1 RV1	RR	0.58	0.28	1.20	18/177	9/51	-
Not reported	RCT	14	A, B, D, E	Europe2 RV1, India RV1, Japan RV1, USA and Canada RV1, Vietnam RV1, Philippines2 RV1,	RR	0.92	0.78	1.09	1115/ 11934	576/ 5433	34%

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
				South Africa2 RV1, Singapore RV1, Latin America3 RV1, Thailand RV1, Philippines1 RV1, Finland3 RV1, Europe1 RV1, USA1 RV1							
Not reported	RCT	5	A, B, D	China RV5, Europe and the Americas RV5, South Korea RV5, Japan RV5, Finalnd and USA RV5	RR	0.90	0.78	1.05	837/ 35204	906/ 35131	4%
Age at 1st dose: mean age in weeks											
7 weeks	RCT	1	E	South Africa2 RV1	RR	1.42	0.76	2.65	17/50	12/50	-
8 weeks	RCT	9	A, B, D	Finland2 RV1, Japan RV1, Philippines1 RV1, Latin America1 RV1, Panama1 RV1, Europe2 RV1, Latin America and Finland RV1, Finland1 RV1, Dominican Republic RV1	RR	0.87	0.81	0.94	1248/ 35241	1203/ 33083	0%
8 weeks	RCT	2	A, D, E	Japan RV5, Africa RV5	RR	0.91	0.62	1.33	48/3113	54/3116	0%
9 weeks	RCT	7	A, B, D	Latin America3 RV1, India RV1, USA and	RR	0.82	0.53	1.28	555/6577	280/2776	24%

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
				Canada RV1, Vietnam RV1, Latin America2 RV1, Finland3 RV1, Thailand RV1							
9 weeks	RCT	4	A, B, D	China RV5, South East Asia RV5, Europe RV5, South Korea RV5	RR	0.67	0.31	1.46	34/1357	37/1307	45%
9 weeks 2nd year	RCT	1	B, D	South East Asia RV5	RR	0.53	0.36	0.78	38/991	71/978	-
10 weeks	RCT	3	B, E	South Africa 3 RV1, Philippines2 RV1, South Korea RV1	RR	0.82	0.33	2.04	20/763	6/212	0%
10 weeks	RCT	2	A, B	Europe and the Americas RV5, Finland and USA RV5	RR	0.93	0.85	1.02	824/ 34685	886/ 34663	0%
11 weeks	RCT	3	A, E	South Africa and Malawi RV1, Europe1 RV1, South Africa1 RV1	RR	0.85	0.75	0.96	639/6244	379/3139	0%
12 weeks	RCT	1	D	Bangladesh RV1	RR	1.51	0.06	36.68	1/200	0/100	-
13 weeks	RCT	2	A	Singapore RV1, USA1 RV1	RR	1.30	0.93	1.82	144/1832	40/673	-

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
Age at last dose: mean age in weeks											
11 weeks	RCT	1	E	South Africa2 RV1	RR	1.42	0.76	2.65	17/50	12/50	-
13 weeks	RCT	3	A, D	India RV1, Finland3 RV1, Japan RV1	RR	0.85	0.61	1.19	78/883	46/485	0%
14 weeks	RCT	1	E	South Africa3 RV1	RR	0.96	0.37	2.51	19/379	5/96	-
15 weeks	RCT	3	B, E	Dominican republic RV1, South Africa1 RV1, Philippines2 RV1	RR	0.96	0.57	1.63	36/681	21/314	0%
16 weeks	RCT	8	A, B, D, E	Philippines1 RV1, Bangladesh RV1, Latin America and Finland RV1, Finland1 RV1, South Africa and Malawi RV1, Panama1 RV1, Finland2 RV1, Europe 2 RV1	RR	0.87	0.81	0.94	1335/ 36513	1278/ 33930	0%
16 weeks	RCT	1	D, E	Africa RV5	RR	0.93	0.62	1.42	42/2733	45/2735	-
17 weeks	RCT	5	A, B, D	Vietnam RV1, USA and Canada RV1, Latin America3 RV1, Thailand RV1, Latin America2 RV1	RR	0.76	0.42	1.35	549/6202	278/2548	47%
18 weeks	RCT	3	A, B, D	Latin America1 RV1, Singapore RV1, South	RR	1.01	0.64	1.61	300/3532	104/1242	78%

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
				Korea RV1							
18 weeks	RCT	1	B, D	South East Asia RV5	RR	1.25	0.70	2.24	25/1017	10/1018	-
20 weeks	RCT	1	A	Europe1 RV1	RR	0.84	0.70	1.00	290/2646	176/1348	-
20 weeks	RCT	1	B, D	Europe RV5	RR	1.25	0.70	2.24	25/1017	20/1018	-
23 weeks	RCT	1	A	USA1 RV1	RR	-	-	-	0/21	0/20	-
24 weeks	RCT	2	A, B	China RV5, Japan RV5	RR	0.48	0.09	2.50	7/404	13/405	37%
29 weeks	RCT	1	B	South Korea RV5	RR	0.47	0.16	1.34	6/115	7/63	-
30 weeks	RCT	2	A, B	Finland and USA RV5, Europe and the Americas RV5	RR	0.93	0.85	1.02	824/ 34685	886/ 34663	0%

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
Co-administration of other vaccines											
Any other vaccine including oral polio vaccine	RCT	7	B, D, E	South Africa2 RV1, Vietnam RV1, Philippines2 RV1, South Africa and Malawi RV1, Bangladesh RV1, South Africa3 RV1, Latin Americas3 RV1	RR	0.92	0.82	1.04	877/8863	473/4216	5%
Any other vaccine including oral polio vaccine	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	1.03	0.73	1.45	67/3750	65/3753	0%
Any other vaccine, including inactivated polio vaccine	RCT	6	A, B	Dominican Republic RV1, Europe2 RV1, USA and Canada RV1, Europe1 RV1, Thailand RV1, Singapore RV1	RR	0.83	0.62	1.11	499/6044	257/2599	52%
Any other vaccine, including inactivated polio vaccine	RCT	1	A, B	Europe RV5	RR	0.50	0.13	1.98	3/201	6/202	-
Any other vaccine, including oral polio vaccine	RCT	1	E	South Africa1 RV1	RR	1.07	0.59	1.96	30/300	14/150	-

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
and inactivated polio vaccine											
Any other vaccine, except oral polio vaccine	RCT	2	A, B	Latin America1 RV1, Latin America and Finland RV1	RR	0.88	0.81	0.95	1084/ 33291	1111/ 32089	0%
Any other vaccine, except oral polio vaccine	RCT	3	A, B, D	South Korea RV5, Europe and the Americas RV5, Finland and USA RV5	RR	0.92	0.84	1.01	830/ 34800	893/ 34726	0%
Any other vaccine, except oral polio vaccine and inactivated polio vaccine	RCT	1	A	Japan RV1	RR	0.83	0.59	1.17	72/508	44/257	-
None allowed	RCT	6	A, B, D	Finland3 RV1, Finland2 RV1, Finland1 RV1, India RV1, USA1 RV1, South Korea RV1	RR	1.50	0.80	2.82	36/894	12/497	0%
None allowed	RCT	1	B	China RV5	RR	0.11	0.01	1.96	0/24	4/24	-
Not reported	RCT	3	B, D	Philippines1 RV1, Panama1 RV1, Latin	RR	0.82	0.29	2.34	26/1007	9/225	16%

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
				America2 RV1							

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio; OPV=oral polio vaccine; IPV=inactivated polio vaccine

D. EVIDENCE ON THE SAFETY OF VARIOUS ROTAVIRUS VACCINE SCHEDULES: RISK OF INTUSSUSCEPTION AFTER ROTAVIRUS VACCINE ADMINISTRATION

TABLE D-I: RISK OF INTUSSUSCEPTION AFTER ROTAVIRUS VACCINES ADMINISTRATION– DATA AFTER EACH VACCINE DOSE, FROM RANDOMISED CONTROLLED TRIALS (RCTS) AND OBSERVATIONAL STUDIES

	Country Ref	Strata	Type of study	Average age at vaccination (mean age)	Method for ascertainment of Intussusception	Days after RV administration	Actual number		Type of esti-mate	Estimate (95% CI)	Remarks
							# / vaccinees	# / placebo			
RCTs	**Dose 1**										
	Latin America and Finland RV1‡‡‡‡‡	A, B	RCT	8-16 weeks	Surgery, autopsy or imaging techniques by independent clinical-events committee.	1-7 days	0/31673	0/31552	-	-	Data is also provided after 42 days up to one year follow up
	Latin America and Finland RV1	A, B	RCT	8-16 weeks		1-42 days	1/31673	2/31552	RR	0.50 (0.05, 5.49)	
	Singapore RV1	A	RCT	8-16 weeks	Ultrasound examination	1-7 days	1/1811	0/653	RR	1.08 (0.04, 26.61)	
	Singapore RV1	A	RCT	8-16 weeks		1-42 days	1/1811	0/653	RR	1.08 (0.04, 26.61)	
	Europe and the Americas RV5§§§§§	A, B, D	RCT	2, 4, 6 or 2, 3, 4 months	Radiography, surgery, or autopsy	1-7 days	0/34821	0/34768	-	-	-

‡‡‡‡‡ Data collected from the FDA report (http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm134142.htm)

§§§§§ Data collected from two FDA reports (http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142304.pdf and http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142306.pdf)

Country Ref	Strata	Type of study	Average age at vaccination (mean age)	Method for ascertainment of Intussusception	Days after RV administration	Actual number		Type of esti-mate	Estimate (95% CI)	Remarks
Europe and the Americas RV5	A, B, D	RCT	2, 4, 6 or 2, 3, 4 months	by independent adjudication committee.	1-42 days	0/17573	1/17502	RR	0.33 (0.01, 8.15)	
Finland1 RV5******	A	RCT	2, 4, 6 months	"diagnosis of intussusception" No further ascertainment.	1-7 days	0/1027	0/332	-	-	-
Finland1 RV5	A	RCT	2, 4, 6 months		1-42 days	1/1027	0/332	RR	0.97 (0.04, 23.91)	
Latin America RV5	B, D	RCT	2, 4, 6 months	Clinical diagnosis, no further details.	1-7 days	0/372	0/363	-	-	Children randomized to OPV+RV5 or RV5 alone
Latin America RV5	B, D	RCT	2, 4, 6 months		1-42 days	0/372	0/363	-	-	
Dose 2										
Latin America and Finland RV1	A, B	RCT	8-16 weeks	Surgery, autopsy or imaging techniques by independent clinical-events committee.	1-7 days	2/29616	2/29465	RR	0.99 (0.14, 7.06)	
Latin America and Finland RV1	A, B	RCT	8-16 weeks		1-42 days	6/29616	6/29465	RR	0.99 (0.32, 3.09)	
Singapore RV1	A	RCT	8-16 weeks	Ultrasound examination	1-7 days	0/1811	0/653	-	-	-
Singapore RV1	A	RCT	8-16 weeks		1-42 days	0/1811	0/653	-	-	-
Europe and the Americas RV5	A, B, D	RCT	2, 4, 6 or 2, 3, 4 months	Radiography, surgery, or autopsy by independent adjudication committee.	1-7 days	1/32773	0/32745	RR	3.00 (0.12, 73.58)	
Europe and the Americas RV5	A, B, D	RCT	2, 4, 6 or 2, 3, 4 months		1-42 days	4/15838	1/15856	RR	4.01 (0.45, 35.84)	
Finland1 RV5	A	RCT	2, 4, 6 months	"diagnosis of intussusception" No further ascertainment.	1-7 days	0/1027	0/332	-	-	-
Finland1 RV5	A	RCT	2, 4, 6 months		1-42 days	0/1027	0/332	-	-	-

****** Information on schedule is suggested by other trials conducted in Europe, not clearly stated on the report of Finland1 RV5.

	Country Ref	Strata	Type of study	Average age at vaccination (mean age)	Method for ascertainment of Intussusception	Days after RV administration	Actual number		Type of esti-mate	Estimate (95% CI)	Remarks
	Latin America RV5	B, D	RCT	2, 4, 6 months	Clinical diagnosis, no further details.	1-7 days	0/372	0/363	-	-	Children randomized to OPV+RV5 or RV5 alone
	Latin America RV5	B, D	RCT	2, 4, 6 months		1-42 days	0/372	0/363	-	-	
	Dose 3										
	Europe and the Americas RV5	A, B, D	RCT	2, 4, 6 or 2, 3, 4 months	Radiography, surgery, or autopsy by independent adjudication committee.	1-7 days	0/31911	0/31810	-	-	-
	Europe and the Americas RV5	A, B, D	RCT	2, 4, 6 or 2, 3, 4 months		1-42 days	2/31631	3/31555	RR	0.76 (0.11, 3.98)	
	Finland1 RV5	A	RCT	2, 4, 6 months	"diagnosis of intussusception" No further ascertainment.	1-7 days	0/1027	0/332	-	-	-
	Finland1 RV5	A	RCT	2, 4, 6 months		1-42 days	0/1027	0/332	-	-	-
	Latin America RV5	B, D	RCT	2, 4, 6 months	Clinical diagnosis, no further details.	1-7 days	0/372	1/363	-	-	Children randomized to OPV+RV5 or RV5 alone
	Latin America RV5	B, D	RCT	2, 4, 6 months		1-42 days	0/372	1/363	-	-	
Obs							**# cases**	**# controls**			
	Dose 1										
	Australia3 RV1-RV5†††††† (RV1 data)	A	Surveillance	2, 4 months	According to Brighton Collaboration definition from questionnaires to	1-7 days	3/154289 doses	0.87 expected‡‡‡‡‡‡	RR	3.45 (0.71, 1.01)	Children's age 1-3 months

†††††† Details of immunization schedule were taken from http://immunise.health.gov.au/. Study stratified by age, number of doses, and state. Calculated the ratio of observed to expected incidence (standardized incidence ratio), which provides an estimated relative risk (RR) under the assumption of constant relative risk within age strata.

‡‡‡‡‡‡ Expected numbers of cases of intussusception post rotavirus vaccine were calculated by multiplying the child-time at risk post-vaccination (i.e. 7 or 21 days per child per vaccine dose), based on the number of children who had received either vaccine during the period of observation, by the estimated background incidence of intussusceptions.

	Country Ref	Strata	Type of study	Average age at vaccination (mean age)	Method for ascertainment of Intussusception	Days after RV administration	Actual number		Type of esti-mate	Estimate (95% CI)	Remarks
ervational	Australia3 RV1-RV5 (RV1 data)	A	Surveillance	2, 4 months	doctors or reported by study nurses.	1-21 days	4/154289 doses	2.61 expected	RR	1.53 (0.42, 3.92)	Children's age 1-3 months
	Australia3 RV1-RV5 (RV1 data)	A	Surveillance	2, 4 months		1-21 days	1/911 doses	0.06 expected	-	-	Children's age 5-7 months
	Australia3 RV1-RV5 (RV5 data)	A	Surveillance	2, 4 months	According to Brighton Collaboration definition from questionnaires to doctors or reported by study nurses.	1-7 days	3/111553 doses	0.57 expected	RR	5.26 (1.09, 15.4)	Children's age 1-3 months
	Australia3 RV1-RV5 (RV5 data)	A	Surveillance	2, 4 months		1-21 days	6/111553 doses	1.71 expected	RR	3.51 (1.29, 7.64)	Children's age 1-3 months
	Australia3 RV1-RV5 (RV5 data)	A	Surveillance	2, 4 months		1-21 days	1/3589 doses	0.13 expected	-	-	Children's age 3-5 months
	USA3 RV5	A	Surveillance	2, 4, 6 months	Level 1 Brighton Collaboration criteria.	1-7 days	11 (Number of doses administered not reported)§§§§§§	13 expected*******	Rate Ratio †††††††	0.83 (0.34, 2.01)	Children's age 6-14 wks
	USA3 RV5	A	Surveillance	2, 4, 6 months		1-7 days	2 (Number of doses administered not reported)	1 expected	Rate Ratio	1.92 (0.22, 7.74)	Children's age 15-23 wks
	USA3 RV5	A	Surveillance	2, 4, 6 months		1-7 days	0 (Number of doses administered not reported)	1 expected	Rate Ratio	0.00 (0.00, 6.01)	Children's age 24-35 wks

§§§§§§ As of August 31, 2007 (data for the study was collected Feb 2006-Sep 2007) the manufacturer had distributed ~9,120,726 doses of RV5 vaccine.

******* The expected number of background cases were calculated by multiplying the background rate of intussusception for each age group (from VSD 2000-2004) by the estimated number of vaccine doses administered (assumed to be equal to the number of doses distributed by the manufacturer) as dose 1, 2, or 3 to infants in that age group.

††††††† Rate ratios (observed/expected)

Country Ref	Strata	Type of study	Average age at vaccination (mean age)	Method for ascertainment of Intussusception	Days after RV administration	Actual number		Type of esti-mate	Estimate (95% CI)	Remarks
USA3 RV5	A	Surveillance	2, 4, 6 months		1-21 days	14 (Number of doses administered not reported)	40 expected	Rate Ratio	0.35 (0.15-0.81)	Children's age 6-14 wks
USA3 RV5	A	Surveillance	2, 4, 6 months		1-21 days	2 (Number of doses administered not reported)	3 expected	Rate Ratio	0.64 (0.07-2.58)	Children's age 15-23 wks
USA3 RV5	A	Surveillance	2, 4, 6 months		1-21 days	0 (Number of doses administered not reported)	2 expected	Rate Ratio	0.00 (0.00-2.01)	Children's age 24-35 wks
USA13 RV5	A	Surveillance	2, 4, 6 months	Brighton Collaboration definition.	1-7 days	1/309,844 doses	0.8 expected‡‡‡‡‡‡‡	SIR§§§§§§§	1.21 (0.03, 6.75)	Number of exposed cases and number of unexposed cases reported
USA13 RV5	A	Surveillance	2, 4, 6 months		1-21 days	7/309,844 doses	5.7 expected	SIR	1.23 (0.50, 2.54)	
Brazil and Mexico RV1	B	Case-control	2,4 months	Surgery, autopsy, contrast enema or ultrasonography by trained coordinators	1-7 days	24/274	17/701	OR	5.8 (2.6, 13.0)	Data from Mexico
Brazil and Mexico RV1	B	Case-control	2,4 months		8-14 days	6/256	17/701	OR	1.1 (0.5–2.7)	Data from Mexico
Brazil and Mexico RV1	B	Case-control	2,4 months		15-21 days	5/255	21/705	OR	0.9 (0.3–2.2)	Data from Mexico
Brazil and Mexico RV1	B	Case-control	2,4 months		1-7 days	4/321	13/1271	OR	1.4 (0.4–4.8)	Data from Brazil
Brazil and Mexico RV1	B	Case-control	2,4 months		8-14 days	6/323	19/1277	OR	1.6 (0.5–4.7)	Data from Brazil

‡‡‡‡‡‡‡ Expected cases of intussusception were based on background rates from VSD 2001-2005 (ICD-9 codes) stratified by age and care site.

§§§§§§§ Standardized incidence ratio, computed by dividing the number of observed visits for intussusceptions following RV5 by the number of expected visits.

Country Ref	Strata	Type of study	Average age at vaccination (mean age)	Method for ascertainment of Intussusception	Days after RV administration	Actual number		Type of esti-mate	Estimate (95% CI)	Remarks
Brazil and Mexico RV1	B	Case-control	2,4 months		15-21 days	3/320	21/1279	OR	0.6 (0.1–2.2)	Data from Brazil
Dose 2										
Australia3 RV1-RV5 (RV1 data)	A	Surveillance	2, 4 months	According to Brighton Collaboration definition from questionnaires to doctors or reported by study nurses.	1-7 days	2/126496 doses	1.9 expected	RR	1.05 (0.13, 3.80)	Children's age 3-5 months
Australia3 RV1-RV5 (RV1 data)	A	Surveillance	2, 4 months		1-21 days	5/126496 doses	5.69 expected	RR	0.88 (0.29, 2.05)	Children's age 3-5 months
Australia3 RV1-RV5 (RV1 data)	A	Surveillance	2, 4 months		1-21 days	1/10993 doses	0.67 expected	-	-	Children's age 5-7 months
Australia3 RV1-RV5 (RV5 data)	A	Surveillance	2, 4 months	According to Brighton Collaboration definition from questionnaires to doctors or reported by study nurses.	1-21 days	1/688 doses	0.03 expected	-	-	Children's age 7-9 months
Australia3 RV1-RV5 (RV5 data)	A	Surveillance	2, 4 months		1-7 days	2/90441 doses	1.5 expected	RR	1.33 (0.16, 4.82)	Children's age 3-5 months
Australia3 RV1-RV5 (RV5 data)	A	Surveillance	2, 4 months		1-21 days	3/90441 doses	4.51 expected	RR	0.67 (0.14, 1.94)	Children's age 3-5 months
USA3 RV5	A	Surveillance	2, 4, 6 months	Level 1 Brighton Collaboration criteria.	1-7 days	1 (Number of doses administered not reported)	0 expected	Rate Ratio	13.6 (0.32-90.8)	Children's age 6-14 wks
USA3 RV5	A	Surveillance	2, 4, 6 months		1-7 days	8 (Number of doses administered not reported)	17 expected	Rate Ratio	0.46 (0.18-1.06)	Children's age 15-23 wks
USA3 RV5	A	Surveillance	2, 4, 6 months		1-7 days	0 (Number of doses administered not reported)	2 expected	Rate Ratio	0.00 (0.00-2.19)	Children's age 24-35 wks

Country Ref	Strata	Type of study	Average age at vaccination (mean age)	Method for ascertainment of Intussusception	Days after RV administration	Actual number		Type of esti-mate	Estimate (95% CI)	Remarks
USA3 RV5	A	Surveillance	2, 4, 6 months		1-21 days	2 (Number of doses administered not reported)	0 expected	Rate Ratio	9.10 (1.00-40.2)	Children's age 6-14 wks
USA3 RV5	A	Surveillance	2, 4, 6 months		1-21 days	18 (Number of doses administered not reported)	52 expected	Rate Ratio	0.35 (0.18-0.67)	Children's age 15-23 wks
USA3 RV5	A	Surveillance	2, 4, 6 months		1-21 days	2 (Number of doses administered not reported)	5 expected	Rate Ratio	0.38 (0.04-1.45)	Children's age 24-35 wks
France RV5	A	Surveillance	2, 3, 4 months	Hospitalized with ICD code of intussusception.	8-21 days	1/4864 (children receiving at least one dose)	NR	-	-	4 cases reported in unvaccinated infants for all doses, not specified further.
USA13 RV5	A	Surveillance	2, 4, 6 months	Brighton Collaboration definition.	1-7 days	1/257915 doses	1.6 expected	SIR	0.62 (0.13, 3.80)	
USA13 RV5	A	Surveillance	2, 4, 6 months		1-21 days	7/257915 doses	7.2 expected	SIR	0.97 (0.39, 2.00)	
Brazil and Mexico RV1	B	Case-control	2,4 months	Surgery, autopsy, contrast enema or ultrasonography by trained coordinators	1-7 days	13/248	34/689	OR	1.1 (0.6–2.2)	Data from Mexico
Brazil and Mexico RV1	B	Case-control	2,4 months		8-14 days	19/254	24/679	OR	2.3 (1.2–4.4)	Data from Mexico
Brazil and Mexico RV1	B	Case-control	2,4 months		15-21 days	18/253	26/681	OR	2.0 (1.0–3.8)	Data from Mexico
Brazil and Mexico RV1	B	Case-control	2,4 months		1-7 days	21/300	50/1169	OR	1.9 (1.1–3.4)	Data from Brazil
Brazil and Mexico RV1	B	Case-control	2,4 months		8-14 days	15/294	70/1189	OR	0.9 (0.5–1.8)	Data from Brazil

	Country Ref	Strata	Type of study	Average age at vaccination (mean age)	Method for ascertainment of Intussusception	Days after RV administration	Actual number		Type of esti-mate	Estimate (95% CI)	Remarks
	Brazil and Mexico RV1	B	Case-control	2,4 months		15-21 days	15/294	72/1191	OR	0.8 (0.4–1.6)	Data from Brazil
	Dose 3										
	Australia3 RV1-RV5 (RV5 data)	A	Surveillance	2, 4 months	According to Brighton Collaboration definition from questionnaires to doctors or reported by study nurses.	1-7 days	0/70994 doses	1.71 expected	-	-	Children's age 3-5 months
	Australia3 RV1-RV5 (RV5 data)	A	Surveillance	2, 4 months		1-21 days	0/70994 doses	1.71 expected	-	-	Children's age 3-5 months
	USA3 RV5	A	Surveillance	2, 4, 6 months	Level 1 Brighton Collaboration criteria.	1-7 days	5 (Number of doses administered not reported)	16 expected	Rate Ratio	0.31 (0.10-0.77)	Children's age 24-35 wks
	USA3 RV5	A	Surveillance	2, 4, 6 months		1-21 days	9 (Number of doses administered not reported)	49 expected	Rate Ratio	0.18 (0.08-0.38)	Children's age 24-35 wks
	France RV5	A	Surveillance	2, 3, 4 months	Hospitalized with ICD code of intussusception.	8-21 days	1/4864 (children receiving at least one dose)	NR	-	-	4 cases reported in unvaccinated infants for all doses, not specified further.
	USA13 RV5	A	Surveillance	2, 4, 6 months	Brighton Collaboration definition.	1-7 days	2/218966 doses	1.9 expected	SIR	1.05 (0.25, 2.36)	
	USA13 RV5	A	Surveillance	2, 4, 6 months		1-21 days	7/218966 doses	8 expected	SIR	0.88 (0.35, 1.81)	

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; RR=risk ratio; NR=not reported.

TABLE D-II: EFFECT OF VARIOUS ROTAVIRUS SCHEDULES ON THE RISK OF INTUSSUSCEPTION - STUDIES STRATIFIED ACCORDING TO WHO MORTALITY STRATUM

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
Vaccine schedule (weeks)											
4, 8, 12 wks	RCT	1	A	Europe RV5	-	-	-	-	0/201	0/202	-
(6), 10, 14 wks	RCT	2	E	South Africa3 RV1, South Africa and Malawi RV1	RR	1.25	0.05	30.76	1/4307	0/1737	-
6, 10, 14 wks	RCT	2	B, D, E	Africa RV5, South East Asia RV5	RR	0.33	0.01	8.17	0/3751	1/3753	-
8, 16 wks	RCT	3	A, B, D	Finland2 RV1, Latin America1 RV1, Latin America and Finland RV1,	RR	0.66	0.33	1.31	14/33561	20/32224	0%
Not reported	RCT	6	A, B	Latin America3 RV1, East Asia RV1, Singapore RV1, Europe1 RV1, Japan RV1, USA and	RR	1.30	0.55	3.08	15/15032	8/9815	0%

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
				Canada RV1							
Not reported	RCT	5	A, B, D	Europe and the Americas RV5********, Finland1 RV5, USA1 RV5, Finland and USA RV5, South Korea RV5	RR	0.69	0.35	1.38	14/36367	19/35162	0%
Age at 1st dose: mean age in weeks											
6 weeks	RCT	1	E	South Africa and Malawi RV1	RR	1.25	0.05	30.76	1/3928	0/1641	-
8 weeks	RCT	4	A, B, D	Latin America and Finland RV1, Latin America1 RV1, Japan RV1, Finland2 RV1	RR	0.66	0.33	1.31	14/34068	20/32481	0%
8 weeks	RCT	1	E	Africa RV5	-	-	-	-	0/2733	0/2735	-

******** Data updated with information from FDA (**www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142306.pdf**). Information is also provided on schedules stating that the USA schedule of vaccination was 2,4,6 months and the European schedule was 2,3,4 months.

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
9 weeks	RCT	2	A, B	Latin America3 RV1, USA and Canada RV1	RR	1.00	0.18	5.47	4/4797	2/2300	-
9 weeks	RCT	3	A, B	South East Asia RV5, South Korea RV5, Europe RV5	RR	0.33	0.01	8.17	0/1334	1/1283	-
10 weeks	RCT	1	E	South Africa3 RV1	-	-	-	-	0/379	0/96	-
10 weeks	RCT	3	A, D	Europe and the Americas RV5, USA1 RV5, Finland and USA RV5	RR	0.68	0.34	1.38	13/35225	19/34777	-
11 weeks	RCT	1	A	Europe1 RV1	RR	1.02	0.09	11.23	2/2646	1/1348	-
12 weeks	RCT	1	A	East Asia RV1	RR	2.00	0.60	6.63	8/5263	4/5256	-
13 weeks	RCT	1	A	Singapore RV1	RR	0.36	0.02	5.77	1/1810	1/654	-
20 weeks	RCT	1	A	Finland1 RV5	RR	0.94	0.04	23.08	1/1027	0/322	-

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
Age at last dose: mean age in weeks											
11 weeks	RCT	1	E	South Africa and Malawi RV1	RR	1.25	0.05	30.76	1/3928	0/1641	-
13 weeks	RCT	1	A	Japan RV1	-	-	-	-	0/507	0/257	-
14 weeks	RCT	1	E	South Africa3 RV1	-	-	-	-	0/379	0/96	-
16 weeks	RCT	2	A, D	Latin America and Finland RV1, Finland2 RV1	RR	0.65	0.32	1.30	13/31943	20/31687	-
16 weeks	RCT	1	E	Africa RV5	-	-	-	-	0/2733	0/2735	-
17 weeks	RCT	2	A, B	Latin America3 RV1, USA and Canada RV1	RR	1.00	0.18	5.47	4/4797	2/2300	-
18 weeks	RCT	3	A, B	Latin America1 RV1, Singapore RV1, East Asia RV1	RR	1.46	0.51	4.13	10/8691	5/6447	0%
18 weeks	RCT	1	B	South East Asia RV5	RR	0.33	0.01	8.17	0/1018	1/1018	-

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
20 weeks	RCT	1	A	Europe1 RV1	RR	1.02	0.09	11.23	2/2646	1/1348	-
20 weeks	RCT	1	A	Europe RV5	-	-	-	-	0/201	0/202	-
26 weeks	RCT	1	A	USA1 RV5	-	-	-	-	0/573	0/148	-
29 weeks	RCT	1	B	South Korea RV5	-	-	-	-	0/115	0/63	-
30 weeks	RCT	2	A, D	Europe and the Americas RV5, Finland and USA RV5	RR	0.68	0.34	1.38	13/34652	19/34629	-
36 weeks	RCT	1	A	Finland1 RV5	RR	0.94	0.04	23.08	1/1027	0/322	-

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
Co-administration of other vaccines											
Any other vaccine including oral polio vaccine	RCT	3	B, E	South Africa and Malawi RV1, Latin America3 RV1, South Africa3 RV1	RR	1.05	0.24	4.71	5/8683	2/3929	0%
Any other vaccine including oral polio vaccine	RCT	2	B, E	South East Asia RV5, Africa RV5	RR	0.33	0.01	8.17	0/3751	1/3753	-
Any other vaccine including inactivated polio vaccine	RCT	3	A	Eureop1 RV1, Singapore RV1, USA and Canada RV1	RR	0.65	0.11	4.01	3/4877	2/2110	0%
Any other vaccine including inactivated polio vaccine	RCT	2	A	Finland1 RV5, Europe RV5	RR	0.94	0.04	23.08	1/1228	0/524	-
Any other vaccine except oral polio vaccine	RCT	4	A, B, D	Latin America and Finland RV1, Latin America1 RV1, East Asia	RR	0.94	0.44	2.04	22/39061	24/37602	32%

Schedule details	Type of study	Number of studies	WHO Mortality stratum	Country and vaccine	Type of estimate	Estimate	Lower 95% CI	Upper 95% CI	n/N Vaccine	n/N Placebo	Hetero-geneity test (I^2)
				RV1, Japan RV1							
Any other vaccine except oral polio vaccine	RCT	4	A, B, D	Europe and the Americas RV5, Finland and USA RV5, USA1 RV5, South Korea RV5	RR	0.68	0.34	1.38	13/35340	19/34840	-
None allowed	RCT	1	A	Finland2 RV1	-	-	-	-	0/270	0/135	-

Blue colour=RV1; orange colour=RV5; purple colour=RV1/RV5. CI=confidence interval; RCT=randomised controlled trial; RR=risk ratio; OPV=oral polio vaccine; IPV=inactivated polio vaccine

Appendices

Rotavirus Vaccines Schedules: A systematic review of safety and efficacy from randomized controlled trials and observational studies of childhood schedules using RV1 and RV5 vaccines

REPORT TO WHO/IVR

Karla Soares-Weiser (MD, PhD)
Enhance Reviews Ltd

Appendices

Contents

Abbreviations

ACIR	Australian Childhood Immunisation Register
ADRAC	Adverse Drug Reactions Advisory Committee
AE	Adverse event
AEFI	Australian passive surveillance data for adverse events following immunisation
ARI	Acute respiratory infection
BIOSIS	Biosciences Information Service of Biological Abstracts
CDC	Centers for Disease Control and Prevention
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Collaboration Trials Register
CI	Confidence Intervals
DARE	Database of Abstracts of Reviews of Effects
DTPa	diphtheria- tetanus- acellular pertussis
ED	Emergency department
ELISA	Enzyme-linked immunosorbent assay
EMBASE	Excerpta Medica Database
EPI	EPI of the Panama Minstry of Health, from Bayard 2011
Exp n	number of expected cases
FDA	Federal Drugs Administration
GE	Gastroenteritis
HepB	Hepatitis B
HiB	Haemophilus influenza B vaccine
HIV	Human immunodeficiency virus
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICTRP	International Clinical Trials Registry Platform
IPV	Inactivated polio vaccine
IR	Incidence Ratio
IRR	Incidence Risk Ratio
IS	Intussusception
ISI	Citation Indexes at Web of Science
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
MEDLINE	Medical Literature Analysis and Retrieval System Online
n	number of events
N	Total number
N*	total number of children with intussusception
nr	Not reported
OR	Odds ratio
PCV	Proportion of cases vaccinated
PPV	Proportion of population vaccinated
RCT	Randomised controlled trial
REST	Rotavirus Efficacy and Safety Trial
RR	Risk Ratio
RRR	Relative Risk Reduction
RT-PCR	Reverse transcriptase polymerase chain reaction
RV	Rotavirus
RV1	Rotarix™; GlaxoSmithKline Biologicals, Rixensart, Belgium
RV5	Rotateq™; Merck, Whitehouse Station,NJ, USA
RVGE	Rotavirus gastroenteritis
SAE	Serious adverse event
SAGE	Strategic Advisory Group of Experts
SCID	Severe combined immunodeficiency
SE	Standard Error
SILAIS	Sistemas Locales de Atencion Integral a la Salud
SIR	Standardized incidence ratio
TGA	Therapeutic Goods Administration
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine efficacy
VSD	Vaccine Safety Datalink
WHO	World Health Organization

Appendix 1: Methods for observational studies review

This systematic review follows the Centre for Reviews and Dissemination guidelines for undertaking systematic reviews[1] and the Cochrane Collaboration Handbook.[2]

Eligibility criteria

We considered observational studies for inclusion with the following designs: (i) non-randomised controlled trials; (ii) controlled before and after studies; (iii) interrupted time series studies; (iv) historically controlled studies; (v) cohort studies; (vi) case-control studies; and (vii) surveillance studies. Due to a lack of studies for some outcomes, we included both studies that described a comparison between two or more groups receiving a licensed rotavirus vaccine and a control group, or within the same group of participants over time[3], and for safety outcomes, also studies that did not have a comparison group.

Studies containing data related to the vaccination of children (up to 18 years) with licensed rotavirus vaccines (RV1 or RV5), were considered for inclusion. For efficacy outcomes, studies were excluded if they did not compare different schedules or serotypes, or if they did not include a comparison group.

The primary safety outcomes of interest were rate of mortality due to gastroenteritis (all cause-diarrhoea) and serious adverse events that were reported as fatal or requiring discontinuation of the vaccine. Secondary safety outcomes were all-cause mortality, serious adverse events as reported by the study authors, and rare adverse events, in particular, intussusception.

The primary efficacy outcomes of interest were severe rotavirus diarrhoea in children receiving: a) different doses of rotavirus vaccine, b) vaccination outside the recommended age range, c) different intervals between doses, or d) rotavirus vaccine co-administered with other childhood vaccines. Secondary efficacy outcomes were hospitalisation or emergency department (ED) visits due to rotavirus diarrhoea with different schedules of rotavirus vaccine (see above) and rotavirus vaccines' effect on severe rotavirus diarrhoea for different G-serotypes.

We planned to examine severe rotavirus diarrhoea for different schedules, but studies only reported on hospitalisations, ED visits, or primary care visits, with a few studies further dividing rotavirus diarrhoea episodes into different severity categories. Therefore, across all observational studies, we defined rotavirus diarrhoea due to hospitalisation, ED visits or primary care visits *as rotavirus diarrhoea related health care encounters*.

Search strategy

Search strategies were developed specifically for each database. We searched the following databases from January 1988 to April 2011 using the search terms and strategy as described in Appendix 2: MEDLINE (1988 to April 2011, update search until February 2012); EMBASE (1988 to April 2011); CDSR, CENTRAL, and DARE published in *The Cochrane Library* (2011, Issue 3); ISI Citation Indexes at Web of Science (ISI) (up to April 2011); LILACS (1988 to April 2011); Uppsala Monitoring System, WHO (up to June 2011). In addition, reference list of the included studies

and citations (ISI) were checked. Furthermore, the Internet was searched via Google Scholar for relevant studies (up to 15 November 2011). We did not limit our search by language. We updated our MEDLINE search monthly, up until February 2012. Additional information on intussusception from a document from the CDC was acquired from a lecture of Professor M Partel at the *Ad-hoc expert consultation on rotavirus vaccine* meeting in Geneva, February 2012.[4]

Study selection

Search results were uploaded to a web-based system (DistillerSR®, www.systematic-review.com). Two reviewers (SG and HB or KSW) independently inspected all titles and abstracts; the full text article was obtained for potentially relevant studies, or in cases of disagreement, and independently inspected. Any disagreement was resolved by consensus. Justifications for excluding studies from the review were documented and are available on request. Figure A1.1 below outlines the process of selecting observational studies.

Data extraction and management

Studies were identified by the name of the vaccine(s), first author and year in which the study was first published. We also extracted detailed information about the comparison used, how participants were allocated to groups, which part of the study was prospective, and on which variables comparability of groups were assessed.[2] Data was collected for the confounding factors considered in the analysis and for the methods used to control for confounding. Because of the need to control for confounding, whenever available, we preferred to extract data for multiple effect estimates, as follows: on the number of people analysed, adjusted and unadjusted effect estimates with their respective measure of variance (standard error (SE), or 95% confidence interval (95%CI)), and the relevant confounding variables that were used to adjust the analysis. We also extracted raw data from contingency tables reporting the number of individuals with the outcome of interest and the total number of individuals in the intervention and control groups, when available.

Assessment of risk of bias in included studies

Risk of bias assessment forms were developed based on published guidelines and checklists[2 3 5 6] Factual information about the potential confounding variables and how researchers dealt with confounding were collected in order to illustrate the extent of heterogeneity between studies. The results of the quality assessment were used for descriptive purposes to provide an evaluation of the overall quality of the included studies.

Measures of treatment effect

Statistical analyses were performed in Stata (*version 12,* "metan" module)[7] combining the point estimates and standard errors in the logarithm scale or the Relative Risk Reduction (RRR, for studies reporting data on diarrhoea mortality) and its 95% confidence interval, using the generic inverse-variance random-effects methods. However, for most of the included studies reported,

data could not be pooled and results were reported narratively. The inverse-variance fixed effect method was also used as a comparison for the overall pooled data.[7]

Subgroup analyses

We planned to examine the effects of two potential variables in the final results: country's child mortality rate, and according to whether children were HIV carriers or not. WHO statistics was used to stratify countries into different mortality strata, A, B, C, D or E, as defined by the WHO.[8] There was not enough data reported in the observational studies to allow subgroup analyses to be performed. Therefore we used data from our Cochrane systematic review of randomised trials.[9] Full details of screening and inclusion criteria are not described here, but can be found in the published review[9] or upon request. For the subgroup analyses on which randomized trials were pooled, we used the DerSimonian and Laird random effects methods. We used z-tests to perform these analyses.

Assessment of statistical heterogeneity

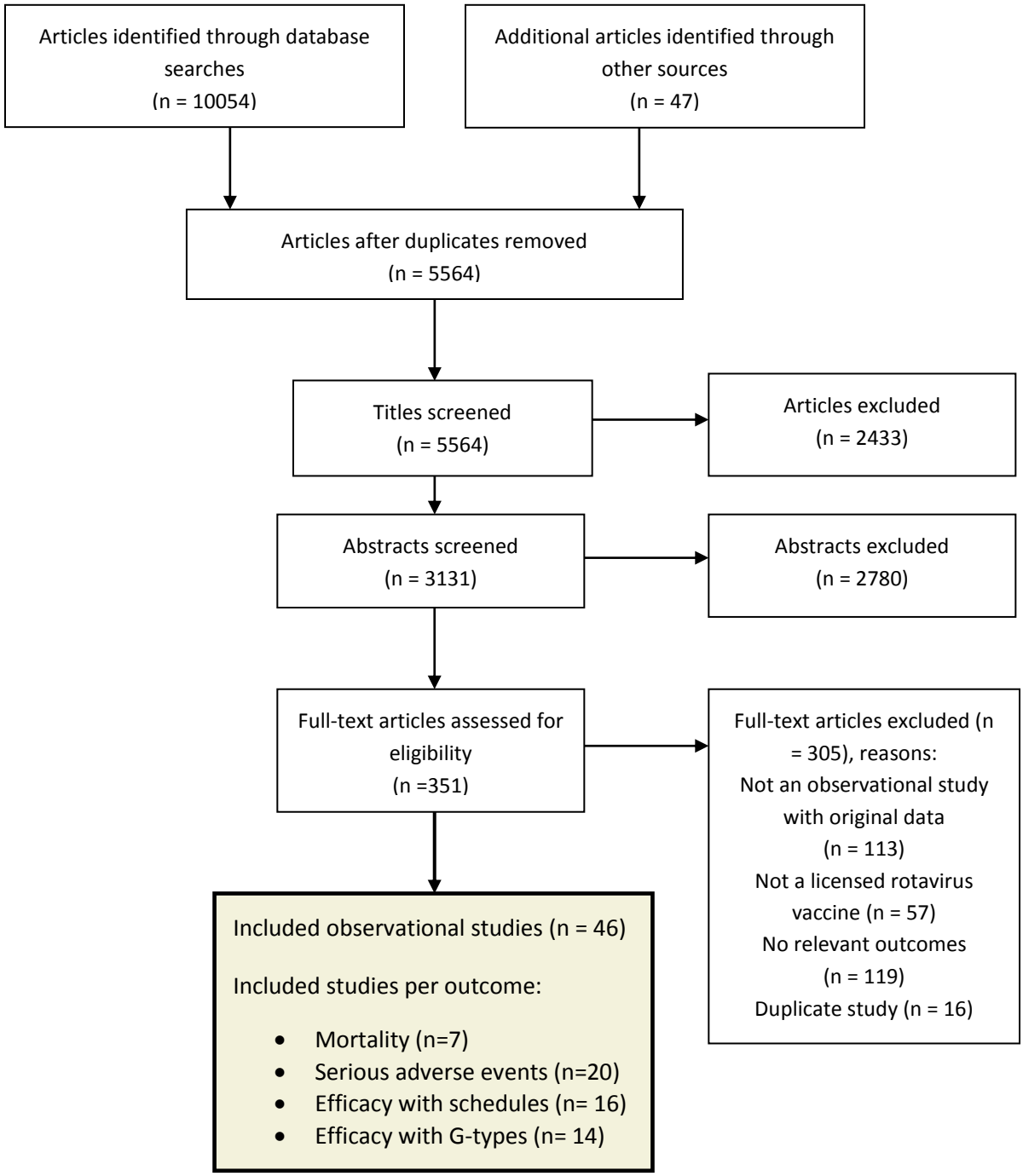
Presence of statistical heterogeneity was assessed only for RCTs using forest plots with Q-test (considered significant for $p<0.10$)[10], and quantified using I^2 (and 95% confidence intervals).[11] In order to further investigate heterogeneity, meta-regression was performed in Stata (version 12, "metareg" module) using the mean age at first dose and country's mortality rate as explanatory variables, and the logarithm of the point estimate as the outcome variable.

The estimate of τ^2 was used to calculate of the proportion of study heterogeneity explained by the covariate (country's children mortality rate), whereasσ^2 was used to represent within study variance.

Grading the evidence

We interpreted the findings of this review using the SAGE recommended GRADE approach [12] and created 'Summary of Findings' tables. These tables provide outcome-specific information concerning the overall quality 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 included in this review.

Figure A1.1: Observational studies screening flow chart



Appendix 2: Observational studies review search strategies

	MEDLINE (PubMed) First searched on 05 April 2011	
#1 [Rotavirus Vaccines terms]	(("RIX4414 vaccine"[Supplementary Concept]) OR (("Rotavirus Vaccines"[Mesh] OR "rhesus rotavirus vaccine"[Supplementary Concept] OR "RotaTeq"[Supplementary Concept] OR "VP3 protein, Rotavirus"[Supplementary Concept] OR "VP2 protein, Rotavirus"[Supplementary Concept] OR "rotavirus vaccine 89-12"[Supplementary Concept] OR "WC3 rotavirus vaccine"[Supplementary Concept] OR "RV3 rotavirus vaccine"[Supplementary Concept] OR "VP1 protein, Rotavirus"[Supplementary Concept] OR "VP6 protein, Rotavirus"[Supplementary Concept] OR "VP7 protein, Rotavirus"[Supplementary Concept] OR "VP4 protein, Rotavirus"[Supplementary Concept]) OR (rotavirus and AND (vaccine OR vaccination OR vaccines)) OR (rotarix OR 89-12) OR (rotateq OR wc3))) OR (RIX4414 OR RV5)	3,489
#2 [Schedules and doses]	Search (schedule OR schedules OR dose OR dosing OR doses) OR ((((((("Maximum Tolerated Dose"[Mesh] OR "Dose-Response Relationship, Immunologic"[Mesh] OR "Dose-Response Relationship, Drug"[Mesh] OR "Immune Tolerance"[Mesh]) OR ("Appointments and Schedules"[Mesh] OR "Drug Administration Schedule"[Mesh] OR "Immunization Schedule"[Mesh])) OR ("Dosage Forms"[Mesh] OR "Desensitization, Immunologic"[Mesh])) OR ("Drug Administration Routes"[Mesh] OR "Administration, Oral"[Mesh] OR "administration and dosage"[Subheading])) OR "Mass Vaccination"[Mesh]) OR "Immunotherapy, Active"[Mesh])	2,111,548
#3 [Combined terms limited to studies performed in humans]	Search #1 AND #2 Limits: Humans	1,121
#4 [Mortality and adverse events]	Search ("Death"[Mesh] OR "Sudden Infant Death"[Mesh] OR "Death Certificates"[Mesh] OR "Death, Sudden, Cardiac"[Mesh] OR "Cause of Death"[Mesh] OR "Death, Sudden"[Mesh] OR "Mortality"[Mesh] OR "mortality"[Subheading]) OR ((("Drug Toxicity"[Mesh]) OR "Adverse Drug Reaction Reporting Systems"[Mesh]) OR ("Safety Management"[Mesh] OR "Risk Management"[Mesh])) OR (toxicity OR (side AND effect) OR (adverse AND effects)) OR (adverse OR side OR toxicity OR intussusception OR bowel OR kawasaki) OR (serious AND adverse) OR (HOSPITAL AND adverse) OR (death OR mortality)	3,122,053
#5 [Combined terms	Search #1 AND #4 Limits: Humans	892

limited to studies performed in humans]		
	MEDLINE (PubMed) Updated on 05 December 2011	
	Search: (("RIX4414 vaccine"[Supplementary Concept]) OR (("Rotavirus Vaccines"[Mesh] OR "rhesus rotavirus vaccine"[Supplementary Concept] OR "RotaTeq"[Supplementary Concept] OR "VP3 protein, Rotavirus"[Supplementary Concept] OR "VP2 protein, Rotavirus"[Supplementary Concept] OR "rotavirus vaccine 89-12"[Supplementary Concept] OR "WC3 rotavirus vaccine"[Supplementary Concept] OR "RV3 rotavirus vaccine"[Supplementary Concept] OR "VP1 protein, Rotavirus"[Supplementary Concept] OR "VP6 protein, Rotavirus"[Supplementary Concept] OR "VP7 protein, Rotavirus"[Supplementary Concept] OR "VP4 protein, Rotavirus"[Supplementary Concept]) OR (rotavirus and AND (vaccine OR vaccination OR vaccines)) OR (rotarix OR 89-12) OR (rotateq OR wc3))) OR (RIX4414 OR RV5)) Limits: Publication Date from 2011/04/01 to 2011/11/16 Sort by: Author	187
	EMBASE (OVID platform) 25 April 2011	
Rotavirus vaccine	1 Rotavirus vaccine/ (2284) 2 Simian rotavirus vaccine/ (115) 3 Rotavirus/ (8480) 4 virus vaccine/ (15685) 5 3 and 4 (317) 6 Rotarix.af. (511) 7 89-12.af. (270) 8 RIX4414.hw. (9) 9 RIX 4414.af. (53) 10 6 or 7 or 8 or 9 (792) 11 Rotateq.af. (497) 12 wc3.af. (69) 13 RV5.af. (178) 14 11 or 12 or 13 (723) 15 Rotavirus.af. (11807) 16 Rota virus.af. (69) 17 15 or 16 (11829) 18 vaccine$.af. (240090) 19 vaccination.af. (123051) 20 18 or 19 (269055) 21 17 and 20 (3722) 22 1 or 2 or 5 or 10 or 14 or 21 (4142)	4,142
Outcomes for schedules	23 dose$.af. (1266676) 24 dose.af. (1123201) 25 doses.af. (341864)	1,672,475

	26	dosing.af. (52495)	
	27	schedule.af. (56815)	
	28	schedules.af. (20464)	
	29	23 or 24 or 25 or 26 or 27 or 28 (1323893)	
	30	DOSE RESPONSE/ (278077)	
	31	MAXIMUM TOLERATED DOSE/ (5750)	
	32	immunological tolerance/ (26677)	
	33	immunization/ (64676)	
	34	drug dosage form/ (8228)	
	35	drug administration route/ (3955)	
	36	oral drug administration/ (319794)	
	37	35 or 36 (323682)	
	38	mass immunization/ (1378)	
	39	IMMUNOTHERAPY/ (38160)	
	40	29 or 30 or 31 or 32 or 33 or 34 or 37 or 38 or 39 (1672475)	
Combined Schedules	41	22 and 40 (1373)	1,373
Outcomes for Safety	42	DEATH/ (71798)	2,222,262
	43	sudden infant death syndrome/ (8302)	
	44	death certificate/ (4961)	
	45	sudden death/ (28110)	
	46	"cause of death"/ (49870)	
	47	MORTALITY/ (367383)	
	48	42 or 43 or 44 or 45 or 46 or 47 (487200)	
	49	drug toxicity/ (31144)	
	50	drug surveillance program/ (11397)	
	51	49 or 50 (42427)	
	52	safety/ (100902)	
	53	risk management/ (22748)	
	54	52 or 53 (121990)	
	55	toxicity.af. (364420)	
	56	side.af. (498165)	
	57	effect.af. (2819487)	
	58	56 and 57 (237323)	
	59	55 or 58 (572241)	
	60	adverse.af. (355823)	
	61	effects.af. (2003041)	
	62	60 and 61 (143513)	
	63	intussusception.af. (8370)	
	64	bowel.af. (100264)	
	65	kawasaki.af. (29678)	
	66	55 or 56 or 60 or 63 or 64 or 65 (1196301)	
	67	serious.af. (163680)	
	68	60 and 67 (25579)	
	69	hospital.af. (3427875)	
	70	60 and 69 (105484)	
	71	death.af. (534661)	
	72	mortality.af. (635060)	

	73 71 or 72 (1042811) 74 48 or 51 or 54 or 59 or 62 or 66 or 68 or 70 or 73 (2222262)	
Combined All	75 40 or 74 (3455809) 76 22 and 75 (2142)	2,142
	The Cochrane Library (Issue 4, 2011)	
Rotavirus vaccine	Terms: ROTAVIRUS vaccin* RESULTS: 274 references WEB: http://www.thecochranelibrary.com/view/0/index.html	274
	ISI Web of Knowledge, 25 April 2011	
Rotavirus vaccine	Terms: ROTAVIRUS VACCIN* RESULTS: 3886 references WEB: http://wok.mimas.ac.uk/	3,886
	LILACS, 25 April 2011	
Rotavirus vaccine	Terms: ROTAVIRUS RESULTS: 607 references WEB: http://lilacs.bvsalud.org/en/	607
	Uppsala Monitoring System, WHO, 8 June 2011	
Rotavirus vaccine	Search terms: Rotavirus vaccine (OR rotateq OR rotarix) RESULTS: 3 references WEB: http://www.who-ums.org	3
	Google Scholar, 7 June 2011(updated on 16 November 2011)	
Rotavirus vaccine AND Outcomes Safety	Search terms: Serious adverse events (with all the words) AND rotarix (exact phrase) = 144 hits Serious adverse events (with all the words) AND rotateq (exact phrase) = 168 hits Rotateq, Rotarix (at least one of the words) AND death (exact phrase) = 252 hits LIMITS: Searched only articles in “Medicine, Pharmacology, and Veterinary Science” Return articles published after 2006 Words may occur anywhere in the article All results were manually inspected by KSW and only the relevant ones were retrieved. In total 47 references were considered relevant and added to the main database.	46 + 1

Appendix 3: Observational studies - description of studies and risk of bias

Table A3.1: Included studies characteristics

Study ID & Reference	Country mortality stratum and rate[1]	No of Children	Study design and data source	Selection Criteria
Panama2 RV1 **RV1 Bayard 2011**[13]	B 20	1222	Historical control using data from the Mortality information system and EPI of the Panama Minstry of Health, with interrupted time-series analysis. Records from 2000 to 2008 collected retrospectively. Molto et al 2011[14] and Guevara et al 2008[15] are companion papers.	Children ≥ 2 months to ≤ 5 years admitted with a diagnosis of acute gastroenteritis were included, pre- and post-RV1 vaccine years were compared. **Vaccine coverage:** 62%-91% received first dose, and 30%-71% received second dose
Brazil3 RV1 **RV1 Carvalho-Costa 2011**[16]	B 19	3802 of 6109 tested were under 5 years	Surveillance study at a hospital in Sao Paulo. Data collected prospectively January 2005 to December 2009. Vieira et al 2011[17] is a companion paper. A small part of study population may overlap with RV1 Gurgel 2009[18].	All in- and outpatients presenting with acute gastroenteritis were screened for rotavirus, children age eligible for vaccination were compared for vaccination status. **Vaccine coverage:** >90% for 1 dose and 82.2% for 2 doses nationally in 2009.
Brazil2 RV1 **RV1 Correia 2010**[19]	B 19	80 cases, 900 controls	Case control study at a teaching hospital in Recife. Data collected prospectively March 2006 to September 2008.	Case patients were children 6 months to 5 years, hospitalised or attending ED for rotavirus gastroenteritis, GE controls were children with rotavirus negative gastroenteritis at hospital, ARI controls were children with acute respiratory infection at hospital. **Vaccine coverage:** 11-13 % for 1 dose, 61-74% for 2 doses (within study population).
El Salvador RV1 **RV1 de Palma 2010**[20]	B 16	323 cases, 969 controls	Case control study in 7 hospitals. Records from January 2007 to June 2009 collected retrospectively.	Case patients were children under 2 years hospitalised for rotavirus gastroenteritis, community controls were date of birth and neighbourhood matched children. **Vaccine coverage:** 21-22% for 1 dose, 47-64% for 2 doses (within study population).
Brazil4 RV1 **RV1 do Carmo 2011**[21]	B 19	2700 annual median diarrhoea related deaths	Historical control study using data from the Mortality information system of the Brazilian Minstry of Health, with interrupted time-series analysis. Records from 2002 to 2009 collected retrospectively. Lanzieri et al 2011[22] and Gurgel et al 2011[23] are companion papers.	Study compared observed cases (post-RV1 vaccine era 2006-2009) to expected cases (pre-vaccine era 2002-2005) of diarrhoea related mortality and all-cause mortality in children ≤ 5 years. **Vaccine coverage:** 80-85% from 2007 to 2009

[1] Mortality strata according to the World Health Organization list of member states (http://www.who.int/whr/2003/en/member_states_182-184_en.pdf). Mortality rate for children ≤5 years per 1000 live births (source: 2010 WHO statistics, Global Health Observatory Data Repository: http://apps.who.int/ghodata/?vid=180)

Study ID & Reference	Country mortality stratum and rate[1]	No of Children	Study design and data source	Selection Criteria
World-wide RV1 **RV1 Escolano 2011**[24]	-	151 cases	Cases-series analysis of spontaneously reported intussusception cases world-wide after RV1 administration. Records from January 2005 to February 2010 collected retrospectively.	Reported cases of intussusception after RV1 vaccination in children with median age 122 days were collected. **Vaccine coverage:** not reported
Brazil1 RV1 **RV1 Gurgel 2009**[18]	B 19	534 hospitalized children	Surveillance study at a hospital in Aracaju, Sergipe state. Data collected prospectively October 2006 to April 2008. Study population may overlap with a small part of RV1 Carvalho-Costa 2011[16].	Children under 10 years old with gastroenteritis at ED were screened for rotavirus and compared for vaccination status. **Vaccine coverage:** 51.5% for 2006, 90.3% for 2007 (Sergipe state).
Brazil5 RV1 **RV1 Justino 2011**[25]	B 19	538 cases, 853 controls	Case control study at four hospitals in Belem. Data collected prospectively May 2008 to May 2009.	Case patients were children 3 to 36 months hospitalised for rotavirus gastroenteritis, hospital controls were age matched children hospitalised for other reasons than gastroenteritis, community controls were age and area of residence matched children. **Vaccine coverage:** 68-85.3% for at least 1 dose and 76.2-85.4% for full 2-dose schedule (within study population).
Brazil and Mexico RV1 **RV1 Patel 2011**[26]	B 19 and 17 respectively	615 cases, 2050 controls	Active surveillance at 69 hospitals with case series and case-control analysis. Prospective enrollment and retrospective review of records from August 2008 to August 2010.	Cases were infants with confirmed intussusception age eligible for RV1 vaccination ≥ 6 to ≤ 35 weeks at the time of diagnosis, community controls were children in the same neighbourhood matched for date of birth (within 30 days before or after). **Vaccine coverage:** 97% case patients and 99% controls had a history of vaccination as confirmed by a vaccination card.
Mexico3 RV1 **RV1 Reyna-Figueroa 2011**[27]	B 17	7,691,757 doses administered, 82 reported SAE cases	Passive surveillance through national system of reporting adverse events after vaccination. Data from January 2008 to December 2009 collected retrospectively.	Reported and later confirmed serious adverse events and cases of intussusception after RV1 vaccination in children 2-7 months were collected. **Vaccine coverage:** not reported
Mexico1 RV1 **RV1 Richardson 2010**[28]	B 17	1793 annual median diarrhoea related deaths pre-vaccine era	Historical control study using data from the National Institute of Statistics, Geography, and Informatics and the Ministry of Health's General Directorate of Health Information. Data from January 2003 to May 2009 collected retrospectively. Includes 2011 update[29] and companion paper Esparza-Aguilar et al 2009[30].	Diarrhoea related mortality after RV1 introduction (2008-2009) in children ≤ 5 years compared to mortality at baseline before vaccine was introduced (2003-2006). **Vaccine coverage:** 74% for dose 1 and 51% for dose 2
Australia1 RV1 **RV1 Snelling 2009**[31]	A 5	173 cases, up to 4 controls per case	Case control study at Alice Springs hospital. Records from March to July 2007 were collected retrospectively.	Case patients were children aged 10 weeks to 5 years hospitalised for gastroenteritis and screened for rotavirus, community controls were date of birth and indigenous status matched children. **Vaccine coverage:** Approximately half of the study cases were vaccinated with at least one dose.
Australia2 RV1 **RV1 Snelling 2011**[32]	A 5	41 cases 164 controls	Case control study at Alice Springs hospital. Data collected prospectively September 2008 to June 2009.	Case patients were children aged 6 weeks to 36 months hospitalised for rotavirus gastroenteritis, population controls were age and indigenous status matched children, hospital controls were children with diarrhoea that tested negative for rotavirus. **Vaccine coverage:** 46-53% of study population were vaccinated with 2 doses.

Study ID & Reference	Country mortality stratum and rate[1]	No of Children	Study design and data source	Selection Criteria
Mexico2 RV1 **RV1 Velazquez 2010**[33]	B 17	459 cases	Active surveillance from 66 hospitals. Data collected prospectively January 2008 to December 2009. Data source could overlap with RV1 Patel 2011[26], results presented in data table.	Temporal association between RV1 dose and intussusception was evaluated in children ≤ 1 year. **Vaccine coverage:** 92.4% received one dose, 57.7% 2 doses
Mexico4 RV1 **RV1 Yen 2011**[34]	B 17	16 cases, 30 controls	Case control study at hospitals in the state of Chiapas. Data collected prospectively March to May 2010.	Cases were children 5 months to 2 years hospitalised with rotavirus gastroenteritis, community controls were healthy children matched for age and municipality. **Vaccine coverage:** >70% for 2 doses.
USA1 RV1-RV5 **RV1-RV5 Bakare 2010**[35]	A 8	9 cases	Passive surveillance from the Vaccine Adverse Events Reporting System. Records from February 2006 to January 2010 collected retrospectively.	Reports of SCID were identified in 3 to 9 months old infants after rotavirus vaccination. **Vaccine coverage:** All cases received vaccine.
Australia3 RV1-RV5 **RV1-RV5 Buttery 2010**[36]	A 5	192 cases	Active surveillance from the Australian Paediatric Surveillance Unit (retrospective) and the Paediatric Active Enhanced Disease Surveillance (prospective), in 4 states. Data collected July 2007 to December 2008 prospectively and retrospectively.	Observed cases of intussusception after rotavirus vaccination in children ≤ 9 months were compared to expected cases based on routinely reported hospitalisation data. **Vaccine coverage:** All observed cases received vaccine.
Latin America and Caribbean RV1-RV5 **RV1-RV5 De Oliveira 2009**[37]	B, D 8 to 51	53484 hospitalised	Sentinel hospital surveillance at 54 sites in 11 Latin American and Carribean countries. Data collected prospectively 2005 to 2007.	Children ≤ 5 years hospitalised with diarrhoea were screened for rotavirus, diarrhoea mortality rates were estimated. **Vaccine coverage:** not reported
USA2 RV1-RV5 **RV1-RV5 Desai 2010**[38]	A 8	84 cases, 84 controls	Case control study at a Connecticut hospital. Data collected prospectively January 2008 to August 2009, and retrospectively from records from March 2006 to December 2007. Less than 10% of study population may overlap with RV5 Cortese 2011[39] and RV5 Guh 2011[40].	Case patients were children 8 weeks to 3 years hospitalised for rotavirus gastroenteritis, hospital controls were age matched children hospitalised for other reasons than rotavirus infection, community controls were age and area of residence matched child **Vaccine coverage:** 12-30% of study population received at least 1 dose.
Germany2 RV1-RV5 **RV1-RV5 Jenke 2011**[41]	A 4	1200 cases	Active surveillance study at all paediatric hospitals in Germany. Data was collected prospectively January 2006 to December 2007.	Children ≤ 15 years with confirmed intussusception diagnosis were included and rotavirus vaccination status was determined. **Vaccine coverage:** not reported
Australia1 RV1-RV5 **RV1-RV5 Lawrence 2008**[42]	A 5	1538 events (90 rotavirus)	Summary of passive surveillance from the Therapeutic Goods Administration. Records from 2007 were collected retrospectively.	Records for children ≤ 7 years were included if a rotavirus vaccine was recorded as 'suspected' of involvement in the reported adverse event. NOTE Rotavirus vaccine was added to the National Immunisation Program schedule on 1 July 2007. **Vaccine coverage:** 219,791 vaccine doses recorded on the Australian Childhood Immunisation Register (ACIR) and administered between 1 January and 31 December 2007.

Study ID & Reference	Country mortality stratum and rate[1]	No of Children	Study design and data source	Selection Criteria
Australia4 RV1-RV5 **RV1-RV5 Mahajan 2011[43]**	A 5	424 events (26 rotavirus)	Summary of passive surveillance in New South Wales from the Therapeutic Goods Administration. Records from 2010 were collected retrospectively.	Records for children ≤ 7 years were included if a rotavirus vaccine was recorded as 'suspected' of involvement in the reported adverse event and if the residential address of the individual was recorded as New South Wales. **Vaccine coverage:** NSW: 77.3% July 2008 and 86.6% Dec 2010
Australia2 RV1-RV5 **RV1-RV5 Menzies 2009[44]**	A 5	1542 events (212 rotavirus)	Summary of passive surveillance from the Therapeutic Goods Administration. Records from 2008 were collected retrospectively.	Records for children ≤ 7 years were included if a rotavirus vaccine was recorded as 'suspected' of involvement in the reported adverse event. **Vaccine coverage:** 514,659 vaccine doses recorded on the Australian Childhood Immunisation Register (ACIR) and administered between 1 January and 31 December 2008.
Israel RV1-RV5 **RV1-RV5 Muhsen 2010[45]**	A 5	111 cases, 216 controls	Case control study at three hospitalis in Israel (Netanya, Hadera, Haifa). Records from November 2007 to December 2009 were collected retrospectively.	Case patients were children below 5 years hospitalised for rotavirus gastroenteritis, GE controls were month and year of birth matched children hospitalised with rotavirus negative gastroenteritis **Vaccine coverage:** 1.8-16.7% within study population.
Germany1 RV1-RV5 **RV1-RV5 Oberle 2010[46]**	A 4	4 cases	Passive surveillance from a German adverse events database. Records from 2001 to June 2010 collected retrospectively.	Reported events of Kawasaki Disease in rotavirus vaccinated children ≤ 6 months. **Vaccine coverage:** not reported
Turkey RV1-RV5 **RV1-RV5 Ozdemir 2010[47]**	B 18	1000 cohort	Cohort study, data source not reported. One companion paper was identified.[48]	Children ≥ 6 to ≤ 36 months vaccinated with rotavirus vaccine were followed for adverse events and rotavirus diarrhoea. **Vaccine coverage:** all 1000 cases received vaccine
Austria RV1-RV5 **RV1-RV5 Paulke-Korinek 2011[49]**	A 4	18 events (until 2008, 2009 not reported)	Passive surveillance study with data from the Austrian Ministry of Health. Records from 2006 to 2009 collected retrospectively. One companion paper was identified.[50]	Records of unconfirmed adverse events after rotavirus vaccination in children ≤ 5 years were included. **Vaccine coverage:** The overall vaccination rate in 2008 was estimated as 72%.
Singapore RV1-RV5 **RV1-RV5 Tan 2009[51]**	A 3	217 cases	Active surveillance study with historical control at one hospital. Records from 1997 to 2007 collected retrospectively.	Cases of intussusception among children ≤ 5 years admitted to hospital were summarized and cases per year, pre- and post-rotavirus vaccine introduction, was estimated. **Vaccine coverage:** 15-18% in 2006; 25% in 2007
Greece RV1-RV5 **RV1-RV5 Trimis 2011[52]**	A 4	2589 hospitalized children	Prospective surveillance study at at tertiary children's hospital in Attica prefecture. Data collected September 2006 to August 2010.	Children under 5 years hospitalised for acute gastroenteritis were screened for rotavirus, children were compared for vaccination status. **Vaccine coverage:** 4% for 2006-07, 25% for 2009-10.
Nicaragua2 RV5 **RV5 Becker-Dreps 2011a[53]**	D 27	32 cases	Historical control study using data collected by the local health ministry in the state of Leon. Records from January 2003 to December 2009 collected retrospectively.	Primary care and hospital records for children ≤ 5 years with diarrhoea were used to estimate mortality due to diarrhoea before and after RV5 vaccine was introduced. **Vaccine coverage:** 61-82%

Study ID & Reference	Country mortality stratum and rate[1]	No of Children	Study design and data source	Selection Criteria
Nicaragua3 RV5 **RV5 Becker-Dreps 2011b[54]**	D 27	392 hospitalized children	Surveillance study at primary health care clinics in the state of Leon. Data collected prospectively April 2008 to March 2009.	Children 10 weeks to 36 months with gastroenteritis at clinic visit were screened for rotavirus and compared for vaccination status. **Vaccine coverage:** 98% for 1 dose, 93% for 2 doses and 77% for 3 doses.
USA6 RV5 **RV5 Begue 2010[55]**	A 8	10,506 hospitalized children	Surveillance study at a large pediatric practice in New Orleans. Records from July 2004 to June 2009 collected retrospectively.	Children < 5 years hospitalised or attending ED for gastroenteritis were screened for rotavirus, children were compared for vaccination status. **Vaccine coverage:** ∼11.1% for 2006-07, 40.3% for 2007-08 and 45.6% for 2008-09.
USA7 RV5 **RV5 Boom 2010[56]**	A 8	117 cases, 692 controls	Case control study at Texas Childrens' Hospital. Data collected prospectively February 2008 to June 2009. Boom et al 2010[57] is a companion paper.	Case patients were children 15 days to 23 months hospitalised or attending ED for rotavirus gastroenteritis, GE controls were children hospitalised with rotavirus negative gastroenteritis, ARI controls were children hospitalised with acute respiratory infection. **Vaccine coverage:** not reported
USA4 RV5 **RV5 Clark 2009[58]**	A 8	712 hospitalized children	Surveillance study with historical control at a hospital in Philadelphia. Records from December 2005 to June 2009 collected retrospectively. Companion papers are Clark et al 2008[59] and Clark et al 2010[60].	Children at hospital for gastroenteritis were screened for rotavirus, pre- and post vaccine eras were compared. **Vaccine coverage:** ∼50% nationwide for 2007, estimated 60% in Philadelphia mid-2008.
USA9 RV5 **RV5 Cortese 2011[39]**	A 8	402 cases, 4845 controls	Case control study at two hospitals in Minnesota, two hospitals in Georgia and one hospital in Connecticut. Records from December 2006 to June 2009 collected retrospectively. Less than 10% of study population may overlap with RV1-RV5 Desai 2010[38] and RV5 Guh 2011[40].	Case patients were children > 8 weeks age eligible to have received RV vaccine, hospitalised or attending ED for rotavirus gastroenteritis, GE controls were children with rotavirus negative gastroenteritis at hospital, community controls were children from the Immunization Information System matched by zip code and birth date. **Vaccine coverage:** 14-48% within study population fully vaccinated.
USA10 RV5 **RV5 Eberly 2011[61]**	A 8	3166 hospitalized children	Historical control study based on the Depatment of Defence's health care system. Records from July 2003 to June 2009 collected retrospectively .	Hospitalization data from military dependents under 5 years were screened for rotavirus gastroenteritis, pre- (2003-2006) and post-vaccine (2007-2009) eras were compared, and vaccinated children were compared to unvaccinated children. **Vaccine coverage:** 54.1% received at least 1 dose during the 2008-2009 season.
Australia2 RV5 **RV5 Field 2010[62]**	A 5	459 hospitalized children (249,257 hospital records screened)	Surveillance study using the Queensland Hospital Admitted Patient Data Collection and the Vaccine Information and Vaccine Administration System. Records from July 2007 to December 2008 were collected retrospectively.	Children 35 weeks to 5 years admitted to hospital for RVGE or GE were checked for vaccination status. **Vaccine coverage:** 73.1% for 3 doses.
France RV5 **RV5 Gagneur 2011[63]**	A 4	4798 cohort	Prospective cohort study with active surveillance at Brest University Hospital, Brittany. Records from May 2007 to May 2009 collected retrospectively. One companion paper was identified.[64]	RV5 vaccinated children ≤ 5 years old were followed for hospitalisations. **Vaccine coverage:** 51.3% received at least one dose and 47.1% received all three doses

Study ID & Reference	Country mortality stratum and rate[1]	No of Children	Study design and data source	Selection Criteria
USA3 RV5 **RV5 Geier 2008**[65]	A 8	1526 events	Summary of passive surveillance from the Vaccine Adverse Event Reporting System. Records from February 2006 to July 2007 collected retrospectively. Haber et al 2008[66] and Hua et al 2009[67] are companion papers.	Adverse event reports following RV5 vaccination in children ≤ 6 months were summarized. **Vaccine coverage:** All reports were of vaccinated children.
USA11 RV5 **RV5 Guh 2011**[40]	A 8	54 cases, 270 controls	Case control study at two hospitals in Connecticut, and using the Connecticut Immunization Registry and Tracking System. Records from July 2006 to December 2008 collected retrospectively. Less than 10% of study population may overlap with RV1-RV5 Desai 2010[38] and RV5 Cortese 2011[39].	Case patients were children age-eligible to receive vaccine, 2 months to 3 years, hospitalised for rotavirus gastroenteritis, community controls were matched by date of birth and town of residence. **Vaccine coverage:** 6-22% of study population had received at least 1 dose.
Nicaragua1 RV5 **RV5 Patel 2009**[68]	D 27	285 cases, 1530 controls	Active surveillance with case control evaluation at four hospitals (in Managua, Jinotepe, Masaya, and Matagalpa). Data collected prospectively June 2007 to June 2008. Mast et al 2011[69] is a companion paper.	Case patients were children age eligible to receive vaccine and under 2 years hospitalised or requiring intravenus hydration for rotavirus gastroenteritis, hospital controls were children matched by date of birth hospitalised for other reasons than gastroenteritis, community controls were matched by date of birth and neighbourhood. **Vaccine coverage**: 55-57% of study population had received 3 doses.
USA8 RV5 **RV5 Patel 2010**[70]	A 8	3 cases	Case series, unknown source. One companion paper was identified.[71]	Description of three children, 2 to 5 months old, diagnosed with SCID after having received RV5. **Vaccine coverage:** All cases were vaccinated.
USA13 RV5 **RV5 Shui 2012**[72]	A 8	786,725 doses administered	Prospective cohort study with active surveillance from the Vaccine Safety Datalink. Data was collected prospectively May 2006 to February 2010. Four companion papers were identified[73-76].	Records of intussusception in children aged ≥ 4 to ≤ 34 weeks who received any dose of RV5 were compared to background incidence. **Vaccine coverage:** 786,725 doses of RV5 administered to the VSD population.
USA12 RV5 **RV5 Staat 2011**[77]	A 8	184 cases, 1004 controls	Case control study at hospital inpatient and emergency department in three medical centers (Tennessee, New York and Ohio states). Data collected prospectively January 2006 to June 2009. Payne et al 2011[78] is a companion paper.	Case patients were children 15 days to 47 months hospitalised or attending ED for rotavirus gastroenteritis, GE controls were date of birth and illness onset matched children with rotavirus negative gastroenteritis at hospital, and ARI controls were date **Vaccine coverage:** 18-54% of study population had received at least 1 dose.
USA5 RV5 **RV5 Uygungil 2009**[79]	A 8	1 case	Case report, unknown source.	Description of one 5 months old child diagnosed with SCID after having received RV5. **Vaccine coverage:** The child was vaccinated.
Australia1 RV5 **RV5 Werther 2009**[80]	A 5	1 case	Case report, unknown source.	Description of one 9 months old child diagnosed with SCID after having received RV5. **Vaccine coverage:** The child was vaccinated.

Table A3.2: Risk of Bias assessment – case control studies

Study	Cases	Controls	Comparability	Exposure to vaccine
Brazil2 RV1 **RV1 Correia 2010** **Country: Brazil** **Design: Case control study** **Data collection: Mar 2006 - Sep 2008** **Age: 6 months – 5 years**	**Adequate definition?** Yes, with independent validation: samples from children treated at hospital for severe diarrhoea were screened for RV. **Representativeness of cases:** Consecutive or obviously representative series of cases: 7am-5pm Mon-Fri all age eligible patients were approached for enrolment.	**Selection of controls:** RV negative diarrhoea hospital controls (children that tested negative for RV) and ARI hospital controls (children hospitalised for acute respitarory infections). **Absence of outcome ascertained:** Partly, ARI controls had "no history of diarrhoea in the preceding 2 weeks".	Study controls for month and year of birth, and age at disease onset.	**Ascertainment of exposure:** Vaccine card review during structured interview blind to case/control status. **Same method for cases and controls?** Yes. **Non response rate:** Similar rate for all groups, 9-11%.
El Salvador RV1 **RV1 De Palma 2010** **Country: El Salvador** **Design: Case control study** **Data collection: Jan 2007 - Jun 2009** **Age: < 2 years**	**Adequate definition?** Yes, with independent validation: samples from children with acute diarrhoea at hospital were screened for RV. **Representativeness of cases:** Consecutive or obviously representative series of cases: healthcare staff notified surveillance coordinator when treating a child under 5 with diarrhoea, admission log was reviewed daily to identify cases of diarrhoea.	**Selection of controls:** Community controls, "interviewers visited homes to the left and right of the case's home until three controls were identified". **Absence of outcome ascertained:** No description of history of outcome.	Study groups matched for date of birth and community; controlled for hospital, socioeconomic status, age, sex, history of breast feeding, daycare attendance and birth weight.	**Ascertainment of exposure:** Clinic secure record or vaccine card review during structured interview, unclear whether blinded to case/control status. **Same method for cases and controls?** Yes. **Non response rate:** Same rate for both groups.
Brazil5 RV1 **RV1 Justino 2011** **Country: Brazil** **Design: Case control study** **Data collection: May 2008 - May 2009** **Age: 3 - 36 months**	**Adequate definition?** Yes, with independent validation: laboratory confirmed RVGE hospitalised children. **Representativeness of cases:** Consecutive or obviously representative series of cases: as part of routine practice samples were collected from all children with diarrhoea and approached for enrolment.	**Selection of controls:** Hospital controls (at hospital for other reasons than diarrhoea or any vaccine perventable disease) and community controls (selected by interviewing neighbours to the left and right of the case home). **Absence of outcome ascertained:** Unclear, "Neighbourhood controls were children without any signs or symptoms of GE..."	Study groups matched for date of birth and neighbourhood.	**Ascertainment of exposure:** Vaccine card review during structured interview, unclear whether blinded to case/control status. **Same method for cases and controls?** Yes. **Non response rate:** No statement.
Australia1 RV1 **RV1 Snelling 2009** **Country: Australia** **Design: Case control study** **Data collection: Mar - Jul 2007** **Age: 10 weeks - 5 years**	**Adequate definition?** Yes, with record linkage to hospital records ICD-codes and subsequently independent validation with immunoassay to confirm RV. **Representativeness of cases:** Consecutive or obviously representative series of cases: medical records for all children admitted to the hospital during the time period were reviewed for enrolment.	**Selection of controls:** Community controls determined from a record of Central Australian births registered on the Northern Territory hospital information database. **Absence of outcome ascertained:** No description of history of outcome.	Study groups matched for community, indigenous status and date of birth (+/-7 days); and controlled for age, doses, remote residence; and stratified by age and doses.	**Ascertainment of exposure:** Secure record: central immunization database. **Same method for cases and controls?** Not described. **Non response rate:** No statement.

Study	Cases	Controls	Comparability	Exposure to vaccine
Australia2 RV1 **RV1 Snelling 2011** **Country: Australia** **Design: Case control study** **Data collection: Sep 2008 - Jun 2009** **Age: 6 weeks - 36 months**	**Adequate definition?** Yes, with independent validation: hospitalised children with RV-confirmed diarrhoea. **Representativeness of cases:** Potential for selection biases: researchers regularly visited the childrens' ward to identify cases.	**Selection of controls:** Population control cohort from immunization register of Central Australia, hospital control group were children hospitalised with diarrhoea that tested negative for RV. **Absence of outcome ascertained:** Yes, controls were taken from cohort where children were removed if hospitalised for RVGE.	Study groups matched for date of birth and indigenous status.	**Ascertainment of exposure:** Secure record, immunization register. **Same method for cases and controls?** Yes. **Non response rate:** No statement.
Mexico4 RV1 **RV1 Yen 2011** **Country: Mexico** **Design: Case control study** **Data collection: Mar - May 2010** **Age: 5 months - 2 years**	**Adequate definition?** Yes, independent validation: children hospitalised with laboratory confirmed RVGE. **Representativeness of cases:** Unclear, not stated.	**Selection of controls:** Community controls, no description of selection. **Absence of outcome ascertained:** No adequate description of history of outcome, it is reported that controls are "healthy" at time of enrolment.	Study groups matched for date of birth and municipality.	**Ascertainment of exposure:** Vaccine card review during structured interview, unclear whether blinded to case/control status. **Same method for cases and controls?** Yes **Non response rate:** No statement.
USA2 RV1-RV5 **RV1-RV5 Desai 2010** **Country: USA** **Design: Case control study** **Data collection: Mar 2006 - Aug 2009** **Age: 8 weeks - 3 years**	**Adequate definition?** Yes, independent validation: children admitted to hospital for laboratory confirmed RVGE. **Representativeness of cases:** Consecutive or obviously representative series of cases: as part of routine practice samples were collected from all children with diarrhoea and approached for enrolment.	**Selection of controls:** Community controls (healthy children attending same medical prectice as cases) and hospital controls (children admitted for other reasons than RV infection). **Absence of outcome ascertained:** Yes, health of controls confirmed by interview and medical record review.	Study groups matched for date of birth, date of hospitalization and attendence at same medical practice, and controlled for illness severity, duration of hospitalisation, and several demographic variables.	**Ascertainment of exposure:** Secure record: medical record review. **Same method for cases and controls?** Yes. **Non response rate:** No statement.
Israel RV1-RV5 **RV1-RV5 Muhsen 2010** **Country: Israel** **Design: Case control study** **Data collection: Nov 2007 - Dec 2009** **Age: < 5 years**	**Adequate definition?** Yes, independent validation: children admitted to hospital for laboratory confirmed RVGE. **Representativeness of cases:** Consecutive or obviously representative series of cases:pediatric wards were surveyed and stool specimens collected from children with diarrhoea.	**Selection of controls:** Hospital controls were children that tested negative for RV. **Absence of outcome ascertained:** Yes, if a child was hospitalised for GE more than once, the earlier admission was included in the analysis.	Study controls for age, season, socioeconomic status, age at admission, hospital, socioeconomic status and birth month and year.	**Ascertainment of exposure:** Structured interview, unclear whether blinded to case/control status. **Same method for cases and controls?** Yes. **Non response rate:** No statement.
USA7 RV5 **RV5 Boom 2010** **Country: USA** **Design: Case control study** **Data collection: Feb 2008 - Jun 2009** **Age: 15 days - 23 months**	**Adequate definition?** Yes, independent validation: children admitted to hospital for laboratory confirmed RVGE. **Representativeness of cases:** Consecutive or obviously representative series of cases: inpatient floors were actively surveyed and age eligible children were offered participation.	**Selection of controls:** GE controls were children with GE that tested negative for RV, ARI controls were children hospitalised for acute respitarory infections. There were also some community controls not included in final analysis. **Absence of outcome ascertained:** No description of history of outcome.	Study controls for age at presentation, month and year of birth, zip code.	**Ascertainment of exposure:** Secure record from immunization provider or local immunization register, and vaccine record from parent during enrolment. **Same method for cases and controls?** Yes. **Non response rate:** Similar rate for all groups, 6-12%.

Study	Cases	Controls	Comparability	Exposure to vaccine
USA9 RV5 **RV5 Cortese 2011** **Country: USA** **Design: Case control study** **Data collection: Dec 2006 - Jun 2009** **Age: > 8 weeks and age eligible to have received rotavirus vaccine.**	**Adequate definition?** Yes, record linkage: ICD-codes for diarrhoea from Immunization Information System database at hospitals in Minnesota, Georgia, Connecticut with and independent validation: hospitalised for laboratory confirmed RVGE. **Representativeness of cases:** Consecutive or obviously representative series of cases: all cases with GE in hospital for the relevant time eligible to have received vaccine and had RV test results available.	**Selection of controls:** GE hospital controls were children with GE that tested negative for RV, and community controls were taken from immunization information system. **Absence of outcome ascertained:** No description of history of outcome.	Study groups matched for date of birth and zip code and controlled for site, season, hospital, insurance status,	**Ascertainment of exposure:** Secure records from vaccine provider and immunization information system. **Same method for cases and controls?** Yes. **Non response rate:** No statement.
USA11 RV5 **RV5 Guh 2011** **Country: USA** **Design: Case control study** **Data collection: Jul 2006 - Dec 2008** **Age: 2 months - 3 years**	**Adequate definition?** Yes, independent validation: children hospitalised for laboratory confirmed RVGE. **Representativeness of cases:** Consecutive or obviously representative series of cases: all cases with RVGE considered for enrolment.	**Selection of controls:** Community controls from immunization registry. **Absence of outcome ascertained:** Yes, controls had not been hospitalised for confirmed RVGE during the study period.	Study groups matched for date of birth and town of residence.	**Ascertainment of exposure:** Secure records from immunization registry. **Same method for cases and controls?** Yes. **Non response rate:** not applicable, controls were taken from the immunization registry used to ascertain vaccine exposure.
Nicaragua1 RV5 **RV5 Patel 2009** **Country: Nicaragua** **Design: Active surveillance study with case control evaluation** **Data collection: Jun 2007 - Jun 2008** **Age: < 2 years**	**Adequate definition?** Yes, independent validation: children admitted or requiring intravenous hydration at hospital for laboratory confirmed RVGE. **Representativeness of cases:** Consecutive or obviously representative series of cases: active, 24 hour surveillance of inpatient ward and ED, staff were encouraged to notify of any GE cases, in addition, the ED and admissions log was consulted.	**Selection of controls:** Community controls were enroled by visiting homes to the left and right of the case home, and hospital controls were children seeking care at hospital for other reasons than diarrhoea or vaccine preventable disease. **Absence of outcome ascertained:** No description of history of outcome.	Study groups matched for date of birth, neighbourhood, and controlled for several demographic variables.	**Ascertainment of exposure:** Vaccine card review during structured interview, unclear whether blinded to case/control status. **Same method for cases and controls?** Yes. **Non response rate:** Vaccine history confirmed for all participants.
USA12 RV5 **RV5 Staat 2011** **Country: USA** **Design: Case control study** **Data collection: Jan 2006 - Jun 2009** **Age: 15 days - 47 months**	**Adequate definition?** Yes, independent validation: children hospitalised or at ED for laboratory confirmed RVGE. **Representativeness of cases:** Consecutive or obviously representative series of cases: active surveillance for children with diarrhoea 5 days of the week for hospitalisations and systematic, random sampling in the ED.	**Selection of controls:** GE hospital controls were children that tested negative for RV, and ARI hospital controls were children hospitalised or seen in the ED for acute respitarory infections. **Absence of outcome ascertained:** No description of history of outcome.	Study groups matched for date of birth and symptom onset date, and controlled for insurance status, site and clinical setting.	**Ascertainment of exposure:** Secure record from vaccine provider or state immunization registry. **Same method for cases and controls?** Yes. **Non response rate:** Different rate for cases (2.2%) compared to controls (9.1%).

Table A3.3: Risk of Bias assessment – other study designs

Study	Selection	Confounders and comparability	Ascertainment of outcomes	Follow-up
Panama2 RV1 **RV1 Bayard 2011** **Country**: Panama **Design:** Historical control study **Data collection:** 2000 and 2008 **Age:** ≥2 months to ≤5 years	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of diarrhoea deaths obtained from the Mortality Information System of the Panama Ministry of Health. **Non-exposed cohort:** Drawn from the same community as the exposed cohort, data from the pre-vaccine period. **Ascertainment of vaccine exposure?** No, data collected from pre- and post-vaccine periods. **Outcomes not present at start:** No description.	Adjusted for age.	Record linkage, national database.	Follow-up, not applicable – historical control study. **Study duration:** 5 years + 2 years
Brazil3 RV1 **RV1 Carvalho-Costa 2011** **Country: Brazil** **Design: Surveillance study** **Data collection: Jan 2005 - Dec 2009** **Age: not specified**	**Representativeness:** Selected group of users, patients presenting at hospital or local health centre with diarrhoea. **Non-exposed cohort:** Drawn from the same community as the exposed cohort. **Ascertainment of vaccine exposure?** No description. **Outcomes not present at start:** No description.	Stratified by age group, geographic region, year, vaccination status and season.	Independent assessment, stool samples analysed with polyacrylamide gel electrophoresis and enzyme immuno-assay kit for RV antigen and RT-PCR for genotyping.	Follow-up not applicable – surveillence study. **Study duration:** 5 years
Brazil4 RV1 **RV1 do Carmo 2011** **Country:** Brazil **Design:** Historical control study **Data collection:** 2002-2009 **Age:** ≤4 years	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of diarrhoea deaths obtained from the Mortality Information System of the Brazilian Ministry of Health. **Non-exposed cohort:** Drawn from the same community as the exposed cohort, data from the pre-vaccine period. **Ascertainment of vaccine exposure?** No, data collected from pre- and post-vaccine periods. **Outcomes not present at start:** No description.	Adjusted for seasonality and secular trends. Stratified by age group (under 1 year, 1 to <2 years, 2 to 4 years), and region of Brazil.	Record linkage, national database.	Follow-up, not applicable – historical control study. **Study duration:** 2 years + 3 years
World-wide RV1 **RV1 Escolano 2011** **Country:** Not specified **Design:** Case series **Data collection:** 2005-2010 **Age:** ≤1 year	**Representativeness:** No description of the derivation of the cases. **Non-exposed cohort:** Case series - no non-exposed cohort. **Ascertainment of vaccine exposure?** No description. **Outcomes not present at start:** No description.	Case series - no non-exposed cohort.	No description.	Follow-up, not applicable – case series. **Study duration:** 5 years
Brazil1 RV1 **RV1 Gurgel 2009** **Country: Brazil** **Design: Surveillance study** **Data collection: Oct 2006 - Apr 2008** **Age: <10 years**	**Representativeness:** Selected group of users, only children attending hospital for diarrhoea. **Non-exposed cohort:** Drawn from the same community as the exposed cohort. **Ascertainment of vaccine exposure?** Yes, vaccination card. **Outcomes not present at start:** No description.	Stratified by time-period, region and diarrhoea severity.	Independent assessment, stool sample tested with enzyme-linked immunosorbent assay (ELISA) for RV antigen and reverse transcriptase polymerase chain reaction (RT-PCR) for genotyping.	Follow-up not applicable – surveillence study. **Study duration:** 1.5 years

Study	Selection	Confounders and comparability	Ascertainment of outcomes	Follow-up
Brazil and Mexico RV1 **RV1 Patel 2011** **Country:** Brazil, Mexico **Design:** Active surveillance (case-series and case-control at 69 hospitals) **Data collection:** 2008-2010 **Age:** ≤9 months	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of intussusception from 53 hospitals in Brazil and 16 hosiptials in Mexico. **Non-exposed cohort:** Drawn from the same community as the exposed cohort. **Ascertainment of vaccine exposure?** Yes, secure records, clinical records and vaccination cards. **Outcomes not present at start:** No description.	Study controls for age, season of birth and regional variations.	Independent assessment, Brighton Collaboration level 1 criteria to validate cases of intussusception	Follow-up not applicable – surveillence study. **Study duration:** 2 years
Mexico3 RV1 **RV1 Reyna Figueroa 2011** **Country:** Mexico **Design:** Passive surveillance **Data collection:** 2008-2009 **Age:** 2-7 months	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of serious adverse events and intussusception from national system of reporting adverse events in Mexico. **Non-exposed cohort:** None. **Ascertainment of vaccine exposure?** No description. **Outcomes not present at start:** No description.	No non-exposed cohort.	Independent assessment, medical records.	Follow-up not applicable – surveillence study. **Study duration:** 2 years
Mexico1 RV1 **RV1 Richardson 2010** **Country:** Mexico **Design:** Historical control study **Data collection**: Jan 2003 – Dec 2009 **Age:** ≤5 years	**Representativeness:** Somewhat representative of the average children receiving rotavirus vaccine in the community, data from National Center for Child and Adolescent Health, which provides vaccine for 50% of Mexican infants. **Non-exposed cohort:** Drawn from a different source, from the National Institute of Statistics, Geography, and Informatics and the Ministry of Health's general Directorate of Health Information. **Ascertainment of vaccine exposure?** No, data collected from pre- and post-vaccine periods. **Outcomes not present at start:** No description.	Stratified by age (0 to 11 months, 12 to 23 months, 24 to 59 months).	Record linkage.	Follow-up, not applicable – historical control study. **Study duration:** 3 years + 2 years
Mexico2 RV1 **RV1 Velazquez 2010** **Country:** Mexico **Design:** Active surveillance **Data collection**: January 2008 to December 2009 **Age:** ≤ 1 year	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, IS cases from 66 Mexican hospitals. **Non-exposed cohort:** Drawn from a different source, based on experience with a previous RV vaccine. **Ascertainment of vaccine exposure?** No description. **Outcomes not present at start:** No description.	No description.	No description, abstract, not enough details provided.	No statement about losses to follow-up. **Study duration:** 2 years
USA1 RV1-RV5 **RV1-RV5 Bakare 2010** **Country:** USA **Design:** Passive surveillance **Data collection:** 2006-2010 **Age:** ≤1 year	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of children who received the vaccine with SCID. **Non-exposed cohort:** Surveillance study - no non-exposed cohort. **Ascertainment of vaccine exposure?** Unclear, self report. However, all serious adverse events and deaths are followed up by the CDC/FDA. **Outcomes not present at start:** No description.	Surveillance study - no control group	Record linkage, VAERS searched for rotavirus vaccintation, "combined immunodeficiency" and "SCID".	Follow-up not applicable – surveillence study. **Study duration:** 4 years

Study	Selection	Confounders and comparability	Ascertainment of outcomes	Follow-up
Australia3 RV1-RV5 **RV1-RV5 Buttery 2010** **Country:** Australia **Design:** Active surveillance **Data collection:** 2007-2008 **Age:** ≤9 months	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of intussusception from the Australian Paediatric Surveillance Unit and Paediatric Active Enhanced Disease Surveillance databases. **Non-exposed cohort:** Drawn from the same community as the exposed cohort, data from the pre-vaccine period. **Ascertainment of vaccine exposure?** Yes, secure record, patient file, parent's records or Australian Childhood Vaccination Register. **Outcomes not present at start:** No description.	Stratified by age, state and number of doses.	Independent assessment, Brighton Collaboration definition.	Follow-up not applicable – surveillence study. **Study duration:** 1.5 years
Latin America and Caribbean RV1-RV5 **RV1-RV5 de Oliveira 2009** **Countries:** Latin America and Caribbean region **Design:** Sentinel hospital surveillance **Data collection:** 2005 – 2007 **Age:** ≤5 years	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, includes all cases of suspected rotavirus infection of children admittd to sentinel hospitals in eleven countries, of which only 3 introduced roatvirus vaccine during the period of analysis. **Non-exposed cohort:** Surveillance study, no control group. **Ascertainment of vaccine exposure?** No, exact or estimates of vaccine coverage not provided. **Outcomes not present at start:** No description.	No description	No description.	Follow-up not applicable – surveillence study. **Study duration:** 3 years
Germany2 RV1-RV5 **RV1-RV5 Jenke 2001** **Country:** Germany **Design:** Active surveillance **Data collection:** 2006-2007 **Age:** ≤15 years	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of intussusception from the German Paediatric Surveillance Unit database. **Non-exposed cohort:** Surveillance study - no non-exposed cohort. **Ascertainment of vaccine exposure?** Yes, secure record, German Paediatric Surveillance Unit surveillance system. **Outcomes not present at start:** No description.	Surveillance study - no non-exposed cohort.	Independent assessment, according to Brighton Collaboration criteria.	Follow-up not applicable – surveillence study. **Study duration:** 2 years
Australia1 RV1-RV5 **RV1-RV5 Lawrence 2008** **Country: Australia** **Design:** Passive surveillance **Data collection:** 2007 **Age:** ≤7 years	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of intussusception from the Australian Adverse Drug Reaction System database. **Non-exposed cohort:** Surveillance study - no non-exposed cohort **Ascertainment of vaccine exposure?** No, a vaccine recorded in the Australian Adverse Drug Reactions System database as 'suspected' of involvement in the reported adverse event. **Outcomes not present at start:** No description.	Surveillance study - no non-exposed cohort.	Record linkage, all reports are assessed using internationally consistent criteria.	Follow-up not applicable – surveillence study. **Study duration:** 1 year

Study	Selection	Confounders and comparability	Ascertainment of outcomes	Follow-up
Australia4 RV1-RV5 **RV1-RV5 Mahajan 2011** **Country:** Australia **Design:** Passive surveillance **Data collection:** 2010 **Age:** ≤7 years	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of intussusception from the Australian Adverse Drug Reaction System database. **Non-exposed cohort:** Surveillance study - no non-exposed cohort. **Ascertainment of vaccine exposure?** No, a vaccine recorded in the Australian Adverse Drug Reactions System database as 'suspected' of involvement in the reported adverse event. **Outcomes not present at start:** No description.	Surveillance study - no non-exposed cohort.	Record linkage, all reports are assessed using internationally consistent criteria.	Follow-up not applicable – surveillence study. **Study duration:** 1 year
Australia2 RV1-RV5 **RV1-RV5 Menzies 2009** **Country:** Australia **Design:** Passive surveillance **Data collection:** 2008 **Age:** ≤7 years	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of intussusception from the Australian Adverse Drug Reaction System database. **Non-exposed cohort:** Surveillance study - no non-exposed cohort. **Ascertainment of vaccine exposure?** No, a vaccine recorded in the Australian Adverse Drug Reactions System database as 'suspected' of involvement in the reported adverse event. **Outcomes not present at start:** No description.	Surveillance study - no non-exposed cohort.	Record linkage, all reports are assessed using internationally consistent criteria.	Follow-up not applicable – surveillence study. **Study duration:** 1 year
Germany1 RV1-RV5 **RV1-RV5 Oberle 2010** **Country:** Germany **Design:** Passive surveillance **Data collection:** 2001-2010 **Age:** ≤6 months	**Representativeness:** Selected group of users, children reported as having Kawasaki disease and vaccination with RV5 or RV1. **Non-exposed cohort:** Surveillance study - no non-exposed cohort. **Ascertainment of vaccine exposure?** No, "structured query language" search for vaccine terms in database for the detection of vaccine complications or side effects. **Outcomes not present at start:** No description.	Surveillance study - no control group	Record linkage, database coded according to the criteria of the WHO. If a case was sufficient for assessment, hospital discharge reports and test results were requested.	No statement about losses to follow-up. **Study duration:** 9 years
Turkey RV1-RV5 **RV1-RV5 Ozdemir 2010** **Country:** Turkey **Design:** Cohort study **Data collection:** not reported **Age:** ≥6 months to ≤36 months	**Representativeness:** No description of the derivation of the cases. **Non-exposed cohort:** No control/non-exposed cohort **Ascertainment of vaccine exposure?** Not reported. **Outcomes not present at start:** No description.	No control group/non-exposed group	No description.	No statement about losses to follow-up. **Study duration:** Not reported.
Austria RV1-RV5 **RV1-RV5 Paulke-Korinek 2011** **Country:** Austria **Design:** Passive surveillance **Data collection:** Data collected for SAEs was for one year 2009, data for hospitalisations from 2001-2005 and 2008-2009 **Age:** ≤5 years	**Representativeness:** Truly representative of the average children receiving rotavirus vaccine in the community, children with RV at 11 sentinel hospitals shown to be representative of both urban and rural areas in Austria **Non-exposed cohort:** Drawn from the same community as the exposed cohort, data from the pre-vaccine era. **Ascertainment of vaccine exposure?** No, spontaneous reporting system of the Austrian Ministry of Health of vaccine associated severe adverse events reported by medical professionals. **Outcomes not present at start:** No description.	Matched for age (<90 days, 90 days to <15 months, 15 to <32 months, 32 to <60 months)	Self report, severe adverse events after medical treatment reported by physicians to the Austrian Ministry of Health.	Follow-up not applicable – surveillence study. **Study duration:** 1 year

Study	Selection	Confounders and comparability	Ascertainment of outcomes	Follow-up
Singapore RV1-RV5 **RV1-RV5 Tan 2009** **Country:** Singapore **Design:** Active surveillance (Historical control at one hospital) **Data collection:** 1997-2007 **Age:** ≤2 years	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, children with intussusception derived from one hospital. **Non-exposed cohort:** Drawn from a different source, statistics published by the Government of Singapore **Ascertainment of vaccine exposure?** No, pre- vs. post-vaccine eras. **Outcomes not present at start:** No description.	Not described.	Record linkage.	Follow-up not applicable – surveillence study. **Study duration:** 11 years
Greece RV1-RV5 **RV1-RV5 Trimis 2011** **Country: Greece** **Design: Surveillance study** **Data collection: Sep 2006 - Aug 2010** **Age: < 5 years**	**Representativeness:** Selected group of users, children attending hospital for diarrhoea. **Non-exposed cohort:** Drawn from the same community as the exposed cohort. **Ascertainment of vaccine exposure?** Not specified, however, it was reported that no participants were vaccinated. **Outcomes not present at start:** No description.	Adjusted for seasonal trends. Stratified by age subgroup and time-period.	Independent assessment, stool sample tested with rapid immuno-chromatography for RV antigen.	Follow-up not applicable – surveillence study. **Study duration:** 4 years
Nicaragua2 RV5 **RV5 Becker-Dreps 2011a** **Country:** Nicaragua **Design:** Historical control study **Data collection:** Jan 2003 – Dec 2009 **Age:** ≤5 years	**Representativeness:** Truly representative of the average children receiving rotavirus vaccine in the community, data from the Sistemas Locales de Atencion Integral a la Salud (SILAIS) for the state of Leon. **Non-exposed cohort:** Drawn from the same community as the exposed cohort, from the pre-vaccine era. **Ascertainment of vaccine exposure?** No, pre- vs. post-vaccine era. **Outcomes not present at start:** No description.	Data stratified by quarters of interest per year (weeks: 1–13, 14–26, 27–39, and 40–52) and controlled for municipality.	Record linkage, reports from health statisticians at primary care centres and hospital and by nurses at small health posts.	Follow-up, not applicable – historical control study. Study duration: 1 year
Nicaragua3 RV5 **RV5 Becker-Dreps 2011b** **Country: Nicaragua** **Design: Surveillance study** **Data collection: Apr 2008 - Mar 2009** **Age: 10 weeks - 36 months**	**Representativeness:** Selected group of users, children receiving care for diarrhoea at primary health clinic. **Non-exposed cohort:** Drawn from the same community as the exposed cohort. **Ascertainment of vaccine exposure?** Yes, medical record. **Outcomes not present at start:** No description.	No description.	Independent assessment, stool sample tested with ELISA for RV antigen and RT-PCR for genotyping.	Follow-up not applicable – surveillence study. **Study duration:** 1 years
USA6 RV5 **RV5 Begue 2010** **Country: USA** **Design: Surveillance study** **Data collection: Jul 2004 - Jun 2009** **Age: < 5 years**	**Representativeness:** Selected group of users, children attending hospital for diarrhoea. **Non-exposed cohort:** Drawn from the same community as the exposed cohort. **Ascertainment of vaccine exposure?** No, hospital database, audit of sample revealed 20% discrepancy between database and clinical vaccination records. **Outcomes not present at start:** No description.	Stratified by season and age group.	Record linkage, ICD-codes from hospital database, laboratory records for RV test (enzyme immune assay).	Follow-up not applicable – surveillence study. **Study duration:** 5 years

Study	Selection	Confounders and comparability	Ascertainment of outcomes	Follow-up
USA4 RV5 **RV5 Clark 2009** **Country: USA** **Design: Historical control study** **Data collection: Dec 2005 - Jun 2009** **Age: not reported**	**Representativeness:** Selected group of users, children hospitalized for diarrhoea. **Non-exposed cohort:** Drawn from the same community as the exposed cohort. **Ascertainment of vaccine exposure?** No, pre-vaccine era compared to post-vaccine era. **Outcomes not present at start:** No description.	No description.	Independent assessment, stool sample tested with ELISA for RV antigen and RT-PCR for genotyping.	Follow-up, not applicable – historical control study. **Study duration:** 3.5 years
USA10 RV5 **RV5 Eberly 2011** **Country: USA** **Design: Historical control study** **Data collection: Jul 2003 - Jun 2009** **Age: ≤ 5 years**	**Representativeness:** Selected group of users, RVGE hospitalised military dependents of varied socioeconomic status and geographical areas. **Non-exposed cohort:** Drawn from the same community as the exposed cohort, pre-vaccine era. **Ascertainment of vaccine exposure?** Yes, military dependents medical database. **Outcomes not present at start:** Yes: "With the exception of five children, all patients were admitted only once for RGE during the first five years of life".	Stratified by region, season and age (<12 months, 1-year olds, 2-year olds, 3-year olds, 4-year olds, <5 years).	Record linkage, ICD-codes from military dependents medical database.	Follow-up, not applicable – historical control study. **Study duration:** 6 years
Australia2 RV5 **RV5 Field 2010** **Country: Australia** **Design: Surveillance study** **Data collection: Jul 2007 – Dec 2008** **Age: 35 weeks – 5 years**	**Representativeness:** Selected group of users, children hospitalized for RVGE or GE. **Non-exposed cohort:** Drawn from the same community as the exposed cohort. **Ascertainment of vaccine exposure?** Yes, national vaccination register. **Outcomes not present at start:** No description.	No description.	Record linkage, ICD-codes from hospital admission data.	Follow-up not applicable – surveillence study. **Study duration:** 1.5 years
France RV5 **RV5 Gagneur 2011** **Country:** France **Design:** Prospective cohort study (active surveillance) **Data collection:** 2007-2009 **Age:** ≤5 years	**Representativeness:** Truly representative of the average children receiving rotavirus vaccine in the community, all infants in Brest city and 7 suburban districts born between February 20, 2007 and December 01, 2008. **Non-exposed cohort:** Surveillance study - no non-exposed cohort. **Ascertainment of vaccine exposure?** Unclear: "A case report form covering [...] vaccination history information was completed for all confirmed rotavirus diarrhea case-patients" **Outcomes not present at start:** No description.	Controlled for epidemic-to-epidemic variation in disease burden, number of hospitalisations and vaccine introduction.	Independent assessment, stools tested using a rapid anitgen detection method (immunochromatographic assay). ICD codes used for intussusception and Kawaski disease.	Loss of follow up unlikely to introduce bias. **Study duration:** 2 years

Study	Selection	Confounders and comparability	Ascertainment of outcomes	Follow-up
USA3 RV5 **RV5 Geier 2008** **Country:** USA **Design:** Passive surveillance **Data collection:** 2006-2007 **Age:** ≤6 months	**Representativeness:** Not representative of the average children receiving rotavirus vaccine in the community, cases of severe adverse events after vaccination from the VAERS database. **Non-exposed cohort:** Surveillance study - no non-exposed cohort. **Ascertainment of vaccine exposure?** No, database containing vaccine associated adverse events reported by various sources including health care providers and vaccine recipients. **Outcomes not present at start:** No description.	Surveillance study - no control group	Self report, symptom fields for specific SAEs (Costart terms intussusception ("intussusception"), gastrointestinal disorders ("*gastro*"), or Kawasaki Disease ("kawasaki's disease")searched through VAERS using Microsoft Access	Follow-up not applicable – surveillence study. **Study duration:** 1.5 years
USA8 RV5 **RV5 Patel 2010** **Country:** USA **Design:** Case series **Data collection:** unknown **Age:** ≤6 months	**Representativeness:** Selected group of users, infants with SCID in whom vaccine-associated disease developed after receipt of rotavirus vaccine. **Non-exposed cohort:** Case series - no non-exposed cohort. **Ascertainment of vaccine exposure?** Yes, secure medical records. **Outcomes not present at start:** Not present.	Case series - no non-exposed cohort.	Independent assessment, stoll sample tested for rotavirus by RT-PCR.	Follow-up – not applicable, case series. **Study duration:** unknown.
USA13 RV5 **RV5 Shui 2012** **Country:** USA **Design:** Prospective cohort study (active surveillance) **Data collection:** May 2006-Feb 2010 **Age**: 4-34 weeks	**Representativeness:** Truly representative of the average children receiving rotavirus vaccine in the community, data form the Vaccine Safety Datalink (VSD). **Non-exposed cohort:** Drawn from the same community as the exposed cohort, from the pre-vaccine era and children receiving other childhood vaccines. **Ascertainment of vaccine exposure?** Yes, secure record of data files from managed care sites. **Outcomes not present at start:** Yes, only first diagnoses of intussuscpetion were included.	Data stratified by VSD site and week of age; and adjusted for age.	Independent assessment, Brighton Collaboration level 1 criteria to validate cases of intussusception.	Follow-up not applicable – surveillence study. **Study duration:** 4 years and Expected number calculated from years 1991 to 2009.
USA5 RV5 **RV5 Uygungil 2009** **Country:** USA **Design:** Case report **Data collection:** unknown **Age:** ≤6 months	**Representativeness:** Selected group of users, infant with SCID in whom vaccine-associated disease developed after receipt of rotavirus vaccine. **Non-exposed cohort:** Case report - no non-exposed cohort. **Ascertainment of vaccine exposure?** Yes, secure medical record. **Outcomes not present at start:** Not present.	Case report - no non-exposed cohort.	Independent assessment, stoll sample tested for rotavirus by RT-PCR.	Follow-up – not applicable, case report. **Study duration:** unknown.
Australia1 RV5 **RV5 Werther 2009** **Country:** Australia **Design:** Case report **Data collection:** unknown **Age:** ≤1 year	**Representativeness:** Selected group of users, infant with SCID in whom vaccine-associated disease developed after receipt of rotavirus vaccine. **Non-exposed cohort:** Case report - no non-exposed cohort. **Ascertainment of vaccine exposure?** Yes, secure medical record. **Outcomes not present at start:** Not present.	Case report - no non-exposed cohort.	Independent assessment, stoll sample tested for rotavirus by RT-PCR.	Follow-up – not applicable, case report. **Study duration:** unknown.

Appendix 4: Observational studies review narrative results tables

Table A4.1: Mortality due to diarrhoea

<table>
<tr><th>Study details</th><th>Results</th><th>What can we learn from this study?</th></tr>
<tr><td>Mexico1 RV1

RV1 Richardson 2010[28]

Country: Mexico
Design: Historical control study
Data collection: Jan 2003 – May 2009
Age: ≤5 years</td><td>
<table>
<tr><th>Age</th><th>Diarrhoea related deaths – Baseline (2003-6)</th><th>Diarrhoea related deaths (2008)</th><th>RR (95% CI)</th></tr>
<tr><td><1 year</td><td>1197</td><td>680</td><td>41 (36-47), p<.001</td></tr>
<tr><td>1 year</td><td>421</td><td>285</td><td>29 (17-39), p<.001</td></tr>
<tr><td>2-5 years</td><td>175</td><td>153</td><td>7 (-14-26), p=0.44</td></tr>
<tr><td>1-5 (Total)</td><td>1793</td><td>1118</td><td>35 (29-39), p<.00</td></tr>
</table>
Published separately[29] were results for 2008 to 2010 showing a continued reduction in diarrhoea-related mortality rates. Compared to an average mortality rate of 18 deaths per 100,000 children in 2003-2006, there was a 46% reduction (95%CI: 42-50) to 9 deaths per 100,000 in 2008-2010 (p<.001). Most of the reduction occurred in children under 2 years of age.
</td><td>After the introduction of RV1 in Mexico, there was a statistically significant decline in children dying from diarrhoea.

Vaccine coverage in Mexico was above 75% during this period and the drop in the number of deaths was more frequent in children ≤2 years of age, who were likely to have been vaccinated.</td></tr>
<tr><td>Brazil4 RV1

RV1 do Carmo 2011[21]

Country: Brazil
Design: Historical control study
Data collection: Jan 2002 – Dec 2009
Age: ≤5 years</td><td>There were 1610 diarrhoea related deaths in the pre-vaccine era (4 years: 2002-2005) compared to 1435 in the post-vaccine era (3 years: 2007-2009), a percentage decline of 22%.
<table>
<tr><th>Age</th><th>Observed (2007-9) Post-vaccine era</th><th>Expected (2002-5) Pre-vaccine era</th><th>% decline in deaths rate (95% CI)</th></tr>
<tr><td><1 year</td><td>1086</td><td>1240</td><td>22 (6-35)</td></tr>
<tr><td>1 year</td><td>232</td><td>280</td><td>28 (6-45)</td></tr>
<tr><td>2-4 years</td><td>116</td><td>100</td><td>4 (3-29)</td></tr>
<tr><td>≤5 (total)</td><td>1435</td><td>1610</td><td>22 (6-44)</td></tr>
</table>
</td><td>After the introduction of RV1 in Brazil, there was a statistically significant decline in children dying from diarrhoea.

The decline in mortality was more frequent in children ≤1 year for which vaccine coverage was approximately 90%.</td></tr>
<tr><td>Panama2 RV1

RV1 Bayard 2011[13]

Country: Panama
Design: Historical control study
Data collection: 2000 and 2008
Age: ≤5 years</td><td>From 2000-2008, 883 diarrhoea related deaths were reported in Panama in children ≤5 years. The mean number of deaths in the pre-vaccine era (6 years: 2000-2005) was 103 (95%CI: 92-112).
<table>
<tr><th>Age</th><th>Observed (2008) Post-vaccine era Mortality rate</th><th>Expected (2000-5) Pre-vaccine era Mortality rate</th><th>% reduction in deaths rate (95% CI)</th></tr>
<tr><td><1 year</td><td>40</td><td>73</td><td>45 (40-51)</td></tr>
<tr><td>1-4 years</td><td>9</td><td>20.3</td><td>54 (48-60)</td></tr>
<tr><td>≤5 (total)</td><td>15.5</td><td>31.1</td><td>50 (46-54)</td></tr>
</table>
</td><td>After the introduction of RV1 in Panama, there was a statistically significant decline in children dying from diarrhoea.

The decline in mortality was more frequent in children ≤1 year for which vaccine coverage was approximately 91% for first and 71% for second dose.</td></tr>
</table>

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; OR=odds ratio; RR=risk ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System

Study details	Results	What can we learn from this study?
Nicaragua2 RV5 **RV5 Becker-Dreps 2011a**[53] **Country:** Nicaragua **Design:** Historical control study **Data collection:** Jan 2003 – Dec 2009 **Age:** ≤5 years	Pre-Rotavirus immunization program era (Jan 2003-Oct 2006): 1.03 per 10,000 child-years (0.64-1.57). Post-Rotavirus immunization program era (Aug 2007-Sep 2009, vaccine coverage: 61-82%): 0.82 per 10,000 child-years (0.38-1.56). Incidence rate ratio comparing pre and post vaccine eras: 0.80 (0.61-1.04) Less than 10 deaths were reported in this study from 2003-2009. Among those, none occurred in children 12-59 months old, although the majority of these children were not eligible for vaccination.	**There was no statistically significant difference in mortality rate for children after RV5 was introduced compared to before vaccine introduction.**
Latin America and Caribbean RV1-RV5 **RV1-RV5 De Oliveira 2009**[37] **Countries:** Latin America and Caribbean region **Design:** Sentinel hospital surveillance **Data collection:** 2005 – 2007 **Age:** ≤5 years	From 2006-2007, a median of 31% of children hospitalized because of diarrhoea had rotavirus disease (N=8,141). 3,492 children ≤5 years old died because of rotavirus infection (1 out of 2874).	**From this study no conclusions can be made regarding the risk of mortality after rotavirus vaccination.** The impact of rotavirus vaccination on mortality was not investigated as only three of the participating countries had introduced vaccination during the study period.
Turkey RV1-RV5 **RV1-RV5 Ozdemir 2010**[47] **Country:** Turkey **Design:** Cohort study **Data collection:** not reported **Age:** ≥6 months to ≤36 months	In a cohort of 1000 vaccinated children (824 RV1, 176 RV5), 16 children had rotavirus infection and none of them died.	**From this study no conclusions can be made regarding the risk of mortality after rotavirus vaccination.** This study had no control group.

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; OR=odds ratio; RR=risk ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System

Table A4.2: All-cause mortality

Study details	Results				What can we learn from this study?
Brazil4 RV1 **RV1 Do Carmo 2011**[21] **Country:** Brazil **Design:** Historical control study **Data collection:** 2002-2009 **Age:** ≤4 years	**Age**	**Observed post-vaccine era (2007-9)**	**Expected (based on pre-vaccine era)**	**Difference**	**All-cause mortality was not an outcome this study aimed to investigate, and no statistical analysis on the effect of vaccination was carried out. However, the study reports a decline in all-cause mortality during the three years following initiation of RV1 in Brazil among children ≤ 1 year and no difference in children 2-4 years compared to unvaccinated children (adjusted data, years 2002-2005).**
	< 1 yr	35	48	-12	
	1 yr	7	11	-4	
	2-4 yr	1	1	0	
Mexico3 RV1 **RV1 Reyna-Figueroa 2011**[27] **Country:** Mexico **Design:** Passive surveillance **Data collection:** 2008-2009 **Age:** 2-7 months	Out of 7,691,757 doses distributed there were 2 confirmed deaths up to 54 days after RV5 vaccination. Data was taken from national passive surveillance. It is compulsory by law to report serious adverse events after vaccination in Mexico.				**From this study no conclusions can be made regarding the risk of serious adverse events after rotavirus vaccination.** 2 all-cause deaths reported after 7,691,757 doses of RV5, no control group reported.

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

Table A4.3: Narrative results of efficacy[2] against rotavirus diarrhoea related health care encounters for one or two doses of RV1 vaccine, or for one, two or three doses of RV5 vaccine for studies not included in the meta-analysis

Study	Results	What can we learn from this study?
Europe and the Americas RV5 **Data collected from post-hoc analysis Dennehy et al 2011[81]** **Country:** International **Design:** Post-hoc analysis of RCT **Data collection:** Jan 2001 – Oct 2004 **Age:** 6 – 12 weeks at randomization	Between doses data and incomplete vaccination regimen data were analysed post-hoc for the international Rotavirus Efficacy and Safety Trial (REST).[82] **Counts (n) / evaluable (N)** **Analysis** | **Dose** | **Vaccinated** | **Placebo** | **% Efficacy# (95% CI)** **Between doses*** | 1 to 2 | 4/29,420 | 32/29,438 | 88 (65 to 97) **Between doses*** | 2 to 3 | 5/29,484 | 41/29,549 | 88 (69 to 96) **Incomplete regimen**** | 1 | nr/2738 | nr/2671 | 18 (<0 to 75) **Incomplete regimen**** | 2 | nr/1202 | nr/1254 | 73 (<0 to 100) *≥14 days post dose 1 to 13 days post dose 2 and from ≥14 days post dose 2 to 13 days post dose 3 for children that received up to 3 doses. **Children that only received one or two doses. #Efficacy as measured by rate reduction in RVGE related hospitalizations and ED visits.	**Efficacy against RVGE related hospitalization and ED visits for RV5 was 88% between dose one and two and between dose two and three.** **Although the estimates were positive, no statistically significant effect was found for children that only received one or two doses.**
Nicaragua3 RV5 **RV5 Becker-Dreps 2011b[54]** **Country: Nicaragua** **Design: Surveillance study** **Data collection: Apr 2008 – Mar 2009** **Age: 10 weeks – 36 months**	392 children seeking treatment for diarrhoea at primary care clinics were enrolled, stool samples were obtained from 403 of 410 diarrhoea episodes, five children who were not able to provide a stool sample were excluded from the analysis. Among those children who tested positive for rotavirus (N=14), • 10 children had received all three doses of the vaccine, • 3 children were partially immunized, and • one child had not received vaccine.	**From this study no conclusions can be made in relation to the effect of different doses of rotavirus vaccine on rotavirus diarrhoea.** Few children tested positive for rotavirus and no analysis was reported for different doses.
France RV5 **RV5 Gagneur 2011[63]** **Country: France** **Design: Prospective cohort study with active surveillance** **Data collection: May 2007 – May 2009** **Age: ≤ 5 years**	One of 1895 infants enrolled who completed the vaccination schedule without deviation was hospitalized for rotavirus diarrhea versus 47 of 2102 infants who were not vaccinated. This yields a relative risk reduction of 98% (95% CI: 83–100%). Three other vaccinated infants were hospitalized for rotavirus diarrhea. One received 3 doses following an inappropriate schedule and two received only one dose of vaccine.	**From this study no conclusions can be made in relation to the effect of different doses of rotavirus vaccine on rotavirus diarrhoea.** Partially vaccinated healthy infants were not reported, no analysis was reported for different doses.

[2] Efficacy as defined by each study.

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

<table>
<tr><th>Study</th><th>Results</th><th>What can we learn from this study?</th></tr>
<tr>
<td>USA 2 RV1-RV5
RV1-RV5 Desai 2010[38]
Country: USA
Design: Case control study
Data collection: Jan 2008 – Aug 2009
Age: 8 weeks – 3 years</td>
<td>
<table>
<tr><th rowspan="2">Vaccination status[#]</th><th rowspan="2">Cases* (%) N=42</th><th colspan="3">Hospital controls* N=80</th><th colspan="3">Community controls* N=73</th></tr>
<tr><th>n (%)</th><th>Efficacy** (95% CI)</th><th>P</th><th>n (%)</th><th>Efficacy** (95% CI)</th><th>P</th></tr>
<tr><td>Not vaccinated</td><td>37 (88.1)</td><td>56 (70.0)</td><td>-</td><td>-</td><td>52 (71.2)</td><td>-</td><td>-</td></tr>
<tr><td>Inomplete vaccine course</td><td>3 (7.1)</td><td>15 (18.8)</td><td>93.2 (41.4-99.2)</td><td>.015</td><td>10. (13.7)</td><td>93.8 (23.0-99.5)</td><td>.031</td></tr>
<tr><td>Complete vaccine course</td><td>2 (4.8)</td><td>9 (11.3)</td><td>96.3 (28.9-99.8)</td><td>.029</td><td>11 (15.1)</td><td>99.1 (78.1-99.9)</td><td>.032</td></tr>
</table>
[#]children were vaccinated with RV1, RV5 or both vaccines.
*Cases: children hospitalized with RVGE; Hospital controls: date of birth and hospitalization matched children hospitalized for other reasons than RV infection; Community controls: date of birth matched children that were not hospitalized attending the same medical practice for routine care.
** adjusted for ethnicity, gender, tobacco exposure and daycare attendance.
</td>
<td>Efficacy against RVGE related hospitalization for an incomplete vaccine course of RV1 or RV5 was over 93% and for a complete vaccine course, over 96%.</td>
</tr>
<tr>
<td>Israel RV1-RV5
RV1-RV5 Muhsen 2010[45]
Country: Israel
Design: Case control study
Data collection: Nov 2007 – Dec 2009
Age: <5 years</td>
<td>
<table>
<tr><th>Doses received*</th><th>Cases** n (%) N=111</th><th>Controls** n (%) N=216</th></tr>
<tr><td>None</td><td>109 (98.2)</td><td>180 (85.7)</td></tr>
<tr><td>1</td><td>1 (0.9)</td><td>12 (5.7)</td></tr>
<tr><td>2</td><td>0</td><td>9 (4.3)</td></tr>
<tr><td>3</td><td>1 (0.9)</td><td>9 (4.3)</td></tr>
</table>
*38 children were vaccinated, 4 received RV1, 10 RV5 and the rest could not report which vaccine.
**Cases: children hospitalized with RVGE; controls: children hospitalized with RVneative diarrhoea matched for month and year of birth.

Compared to unvaccinated children, the risk of RVGE-associated hospitalization was significantly lower among children vaccinated with:
• at least one dose, OR: 0.106 (95% CI: 0.024-0.481)
• 2-3 doses, OR: 0.113 (95% CI: 0.014-0.932)
</td>
<td>A larger proportion of RV negative children were vaccinated with 1, 2 or 3 doses compared to RV positive children hospitalised with rotavirus diarrhoea, no statistical analysis was reported to demonstrate significance.</td>
</tr>
</table>

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

Table A4.4: Serious Adverse Events

<table>
<tr><th>Study details</th><th>Results</th><th>What can we learn from this study?</th></tr>
<tr>
<td>Austria RV1-RV5

RV1-RV5 Paulke-Korinek 2010[49 50]

Country: Austria
Design: Passive surveillance
Data collection: 2006-2009
Age: ≤5 years</td>
<td>Data from the Austrian Ministry of Health following rotavirus vaccine immunization were reported for the following periods:
<table>
<tr><th>Period</th><th></th><th>RV1</th><th>RV5</th><th>RV1 and RV5</th></tr>
<tr><td rowspan="2">09/2006 – 12/2008</td><td>AEs / administered doses</td><td>5/164,500</td><td>12/112,240</td><td>18*/276,740
10 SAEs</td></tr>
<tr><td>Incidence AEs</td><td>3.0 x 10^{-5}</td><td>10.7 x 10^{-5}</td><td>6.5 x 10^{-5}
SAEs: 3.6 x 10^{-5}</td></tr>
<tr><td rowspan="2">01-12/2009</td><td>AEs / children vaccinated</td><td>nr/5358</td><td>nr/3981</td><td>9/9339</td></tr>
<tr><td>Incidence AEs</td><td>-</td><td>-</td><td>5.4 x 10^{-5}</td></tr>
</table>
*In one case type of vaccine not known
Among the 9 adverse events reported in 2009 there was one case of Kawasaki and one death.
</td>
<td>From this study no conclusions can be made regarding the risk of serious adverse events after rotavirus vaccination.

This study reports a low incidence of SAEs in children vaccinated with RV1 or RV5 after more than 250,000 doses were administered. This study had no control group.

In Austria, physicians are obliged by law to report any severe adverse events after medical treatment to the Ministry of Health.</td>
</tr>
<tr>
<td>Australia4 RV1-RV5

RV1-RV5 Mahajan 2011[43]

Country: Australia
Design: Passive surveillance
Data collection: 2010
Age: ≤7 years</td>
<td>Australian passive surveillance data for adverse events following immunisation (AEFI) reported to the Therapeutic Goods Administration (TGA) for 2010:
After 168,669 administered rotavirus vaccine doses there were 26 reports of adverse events at a reporting rate of 15.4 per 100,000 doses;
10 (38%) of them were serious adverse events.
</td>
<td>From this study no conclusions can be made regarding the risk of serious adverse events after rotavirus vaccination.

10 SAEs reported after 168,669 doses of rotavirus vaccine, no control group reported.</td>
</tr>
<tr>
<td>Australia2 RV1-RV5

RV1-RV5 Menzies 2009[44]

Country: Australia
Design: Passive surveillance
Data collection: 2008
Age: ≤7 years</td>
<td>Australian passive surveillance data for AEFI reported to the TGA for 2008:
After 514,659 administered rotavirus vaccine doses there were 282 reports of adverse events at a reporting rate of 41.0 per 100,000 doses;
50 (24%) of them were serious adverse events.
</td>
<td>From this study no conclusions can be made regarding the risk of serious adverse events after rotavirus vaccination.

50 SAEs reported after 514,659 doses of rotavirus vaccines, no control group reported.</td>
</tr>
</table>

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

Study details	Results	What can we learn from this study?
Australia1 RV1-RV5 **RV1-RV5 Lawrence 2008**[42] **Country:** Australia **Design:** Passive surveillance **Data collection:** 2007 **Age:** ≤7 years	Australian passive surveillance data for AEFI reported to the TGA for from July to December 2007 (the period where the vaccine was included in the funded National Immunisation Program schedule): • After 219,791 administered rotavirus vaccine doses there were 72 reports of adverse events at a reporting rate of 33.2 per 100,000 doses; • 19 (26%) of them were serious adverse events	**From this study no conclusions can be made regarding the risk of serious adverse events after rotavirus vaccination.** 19 SAEs reported after 219,791 doses of rotavirus vaccines, no control group reported.
USA1 RV1-RV5 **RV1-RV5 Bakare 2010**[35] **Country:** USA **Design:** Passive surveillance **Data collection:** 2006-2010 **Age:** ≤1 year	The VAERS database was searched for reports of Severe combined immunodeficiency (SCID) occurring after rotavirus vaccination: • Nine reports of SCID and rotavirus vaccination in infants between 3 and 9 months of age were reported. • 7 children were vaccinated with RV5, one with RV1, and the vaccination status of another one was unknown. Vaccination occurred 1-33 days before hospitalization. • All infants were hospitalized and had workups leading to the SCID diagnosis. Stool rotavirus testing was positive in all cases and the virus was identified as the vaccine strain in six cases. Prolonged viral shedding was documented in five cases. No deaths were reported.	**Although congenital, SCID was not diagnosed in these infants until after rotavirus vaccination, rotavirus vaccination seems to be associated with worsening of symptoms in these children. Earlier identification of SCID (e.g., from expanded newborn screening or heightened clinical vigilance) could prevent inadvertent live rotavirus vaccine administration.**
Germany1 RV1-RV5 **RV1-RV5 Oberle 2010**[46] **Country:** Germany **Design:** Passive surveillance **Data collection:** 2001-2010 **Age:** ≤6 months	Four Kawasaki disease adverse events after vaccination with RV5 were reported to a national passive surveillance database. No clustering regarding age, gender and time to onset of the adverse drug reaction was revealed.	**Few cases of Kawasaki disease were reported after vaccination and no clustering regarding age, gender or time to onset was revealed. It was not possible to establish an accurate relationship between vaccine use and the reported SAEs.**
Mexico3 RV1 **RV1 Reyna-Figueroa 2011**[27] **Country:** Mexico **Design:** Passive surveillance **Data collection:** 2008-2009 **Age:** 2-7 months	Out of 7,691,757 doses distributed there were 82 reported cases of adverse events up to 54 days after RV5 vaccination. Data was taken from national passive surveillance. It is compulsory by law to report serious adverse events after vaccination in Mexico. 22 cases were confirmed to be adverse events and described as 1 light, 6 moderate and 15 serious.	**From this study no conclusions can be made regarding the risk of serious adverse events after rotavirus vaccination.** 15 SAEs reported after 7,691,757 doses of RV5, no control group reported.

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

<table>
<tr><th>Study details</th><th>Results</th><th>What can we learn from this study?</th></tr>
<tr><td>Panama2 RV1

RV1 Bayard 2011, data from companion paper Guevara et al 2008[15]

Country: Panama
Design: Historical control study
Data collection: 2005 and 2007
Age: ≥2 months to ≤5 years</td><td>Complications in children hospitalized because of diarrhoea:

<table><tr><th>Pre-vaccine (2005)</th><th>Post-vaccine (2007)</th><th>RR (95%CI)</th><th>p-value</th></tr><tr><td>30/472 (6.2%)</td><td>47/750 (6.2%)</td><td>1.01 (0.75-1.34)</td><td>0.9</td></tr></table></td><td>Serious adverse events were not reported, data comparing complications before and after the vaccine being introduced showed no statistically significant difference.</td></tr>
<tr><td>USA13 RV5

RV5 Shui 2012, data from companion paper Belongia et al. 2010[73]

Country: USA
Design: Prospective cohort study (active surveillance)
Data collection: 2006-2008
Age: ≤1 year</td><td>Serious adverse events in children ≤1 year of age were sought for in the Vaccine Safety Datalink, occurring up to 1 month after RV5 vaccination. Age adjusted OR comparing RV5 vaccinated to RV5 unvaccinated children:

<table><tr><th>Serious adverse events</th><th>Observed events*</th><th>Expected events**</th><th>Relative Risk</th><th>OR (95% CI) (age adjusted)</th></tr><tr><td>Meningitis and encephalitis</td><td>8</td><td>13.09</td><td>0.61</td><td>-</td></tr><tr><td>Seizures</td><td>38</td><td>56.47</td><td>0.67</td><td>-</td></tr><tr><td>Myocarditis</td><td>0</td><td>0.41</td><td>0.00</td><td>-</td></tr><tr><td>Gram-negative sepsis</td><td>3</td><td>5.65</td><td>0.53</td><td>-</td></tr><tr><td>Kawasaki syndrome</td><td>-</td><td>-</td><td>-</td><td>0.28 (0.07-1.09)</td></tr><tr><td>Gastrointestinal bleeding</td><td>-</td><td>-</td><td>-</td><td>1.11 (0.9-1.37, p=.34)</td></tr><tr><td>Intussusception***</td><td>5</td><td>6.75</td><td>0.74</td><td>-</td></tr></table>*based on electronic diagnoses codes prior to medical record validation
**expected events calculated based on adverse events reported 1991 - 2004 for uncommon, and 2000 to 2004 for common
*** only 2 cases were confirmed</td><td>Few serious adverse events were reported after vaccination and no statistically significant increased risk was observed after RV5 vaccination. It was not possible to establish an accurate relationship between vaccine use and the reported serious adverse events.</td></tr>
</table>

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

Study details	Results	What can we learn from this study?
France RV5 **RV5 Gagneur 2011**[63] **Country:** France **Design:** Prospective cohort study (active surveillance) **Data collection:** 2007-2009 **Age:** ≤5 years	Among 4684 infants who received at least one dose of rotavirus vaccine, 229 serious adverse events were reported and classified as such because these infants were hospitalized within 6 weeks of the last dose. Diagnoses were infectious diseases (56%) and gastrointestinal disorders (17%). No case of Kawasaki and 2 cases of intussusception were reported.	**From this study no conclusions can be made regarding the risk of serious adverse events after rotavirus vaccination.** Serious adverse events were reported in 5% of vaccinated children, but it was unclear whether they were vaccine related. This study had no control group.
USA3 RV5 **RV5 Geier 2008**[65] **Country:** USA **Design:** Passive surveillance **Data collection:**2006-2007 **Age:**≤6 months	The VAERS database is a passive surveillance tool maintained jointly by the CDC and FDA, on which physicians, parents and the public report adverse events of vaccines. Following RV5 administration with or without other vaccines, 1526 adverse events were reported to the VAERS database by July 2007. Among these, 316 led to hospitalization, 84 were considered life threatening, and 14 led to disability. In addition, 160 cases were of intussusception, 97 gastrointestinal disorders, 11 Kawasaki Disease, and 34 deaths.	**From this study no conclusions can be made regarding the risk of serious adverse events after rotavirus vaccination.** As adverse events were in part reported spontaneously by the public, it is not possible to establish an accurate relationship between vaccine use and the reported SAEs. This study had no control group.
USA8 RV5 **RV5 Patel 2010**[70] **Country:** USA **Design:** Case series **Data collection:** unknown **Age:** ≤6 months	Description of three children diagnosed with SCID after having received RV5: • Girl, 5 months old, hospitalized one month after second dose with dehydration, severe diarrhoea, metabolic acidosis, failure to thrive and pneumonia. SCID was diagnosed and treatment given. Stools positive for rotavirus, very ill with diarrhoea at 8 months, stools remained rotavirus positive until the age of 10 months. • Boy, 4 months old, 6 days after second dose presented with shock, dehydration, and watery diarrhoea. Stools were positive for rotavirus. SCID was diagnosed and stem-cell transplantation performed at 5 and at 8 months. Stools remained positive for rotavirus at 8 months, negative at 9 – 12 months. • Boy, 2 months old, presented with severe diarrhoea, failure to thrive and respiratory distress after first dose. Stools were positive for rotavirus. SCID was diagnosed. Bone-marrow transplantation was performed at 8 and at 10 months, at 14 months stools were negative for rotavirus and the diarrhoea had improved.	**Although congenital, SCID was not diagnosed in these infants until after rotavirus vaccination, rotavirus vaccination seems to be associated with worsening of symptoms in these children. Earlier identification of SCID (e.g., from expanded newborn screening or heightened clinical vigilance) could prevent inadvertent live rotavirus vaccine administration.**

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

Study details	Results	What can we learn from this study?
USA5 RV5 **RV5 Uygungil 2009**[79] **Country:** USA **Design:** Case report **Data collection:** unknown **Age:** ≤6 months	• Boy aged 5 months presented to hospital with lethargy, dehydration, and failure to thrive after having received two RV5 doses. Stool tested positive for rotavirus vaccine strains. SCID was diagnosed. One month later he still demonstrated rotavirus in stool.	**Although congenital, SCID was not diagnosed in this infant until after rotavirus vaccination, rotavirus vaccination seems to be associated with worsening of symptoms in these children. Earlier identification of SCID (e.g., from expanded newborn screening or heightened clinical vigilance) could prevent inadvertent live rotavirus vaccine administration.**
Australia1 RV5 **RV5 Werther 2009**[80] **Country:** Australia **Design:** Case report **Data collection:** unknown **Age:** ≤1 year	• Fully immunized (including RV5, 3 doses) girl aged 9 months presented with a history of faltering growth and chronic diarrhoea. She had mild diarrhoea after the first dose of RV5 and remained well until 4 months of age at which time she developed persistent vomiting and diarrhoea with poor weight gain, worsening at 6 month. At 9 months stool tested positive for rotavirus vaccine strains. SCID was diagnosed. At 11 months she received cord blood transplantation. Clear for rotavirus post transplant, but detected again at 13.5 months.	**Although congenital, SCID was not diagnosed in this infant until after rotavirus vaccination, rotavirus vaccination seems to be associated with worsening of symptoms in these children. Earlier identification of SCID (e.g., from expanded newborn screening or heightened clinical vigilance) could prevent inadvertent live rotavirus vaccine administration.**

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

Table A4.5a: Cases of intussusception with RV1

RV1 Study details	Age Time after dose	Dose 1				Dose 2				What can we learn from this study?
Brazil and Mexico RV1 **RV1 Patel 2011**[26] **Country:** Brazil, Mexico **Design:** Active surveillance (case-series and case-control at 69 hospitals) **Data collection:** 2008-2010 **Age:** ≤9 months		Case n/N* (%)	Control n/N (%)	IR (95% CI)	OR (95% CI)	Case n/N* (%)	Control n/N (%)	IR (95% CI)	OR (95% CI)	**A statistically significant increase of intussusception cases was reported for vaccinated infants in Mexico after the first dose up to 7 days after vaccination and after the second dose 8-21 days after vaccination, and in Brazil after the second dose up to 7 days after vaccination.** RV1 was associated with a short-term risk of intussusception in approximately 1 of every 51,000 to 68,000 vaccinated infants. In Mexico, about 13% were vaccinated at older than 14 weeks of age. There was no statically significant interaction by age at vaccination. Children less than 14 weeks of age had a relative risk of 3.6 and those older than 14 weeks had a risk of 5.[4]
	6-35 weeks Mexico:									
	1-7 days	24/274 (9)	17/701 (2)	5.3 (3.0–9.3)	5.8 (2.6–13.0)	13/248 (5)	34/689 (5)	1.8 (0.9–3.8)	1.1 (0.6–2.2)	
	8-14 days	6/256 (2)	17/701 (2)	1.1 (0.5–2.7)	1.0 (0.4–2.9)	19/254 (7)	24/679 (4)	2.2 (1.1–4.2)	2.3 (1.2–4.4)	
	15-21 days	5/255 (2)	21/705 (3)	0.9 (0.3–2.2)	0.8 (0.3–2.1)	18/253 (7)	26/681 (4)	2.2 (1.2–4.0)	2.0 (1.0–3.8)	
	Brazil:									
	1-7 days	4/321 (1)	13/1271 (1)	1.1 (0.3–3.3)	1.4 (0.4–4.8)	21/300 (7)	50/1169 (4)	2.6 (1.3–5.2)	1.9 (1.1–3.4)	
	8-14 days	6/323 (2)	19/1277 (1)	1.3 (0.5–3.4)	1.6 (0.5–4.7)	15/294 (5)	70/1189 (6)	1.4 (0.7–3.0)	0.9 (0.5–1.8)	
	15-21 days	3/320 (1)	21/1279 (2)	0.2 (0.0–1.4)	0.6 (0.1–2.2)	15/294 (5)	72/1191 (6)	0.9 (0.4–2.0)	0.8 (0.4–1.6)	
Australia3 RV1-RV5 **RV1-RV5 Buttery 2011**[36] **Only data on RV1 vaccine** **Country:** Australia **Design:** Active surveillance **Data collection:** 2007-2008 **Age:** ≤9 months		Cases (n/N)	Expected n	RR (95% CI)		Cases (n/N)	Expected n	RR (95% CI)		**The study found a statistically non-significant excess of intussusception cases observed compared to expected for children aged 1-3 months after the first dose up to 7 days and up to 21 days after vaccination.** 302,455 children were vaccinated with RV1, the overall RR for intussusception was 1.58 (95%CI 0.51-3.69) for 7 days and 1.37 (95%CI 0.73-2.34) for 21 days after vaccination. It is likely this data overlaps with RV1-RV5 Lawrence 2008[42] & RV1-RV5 Menzies 2009[44].
	1-3 months									
	1-7 days	3/154289	0.87	3.45 (0.71, 10.1)		0/252	0			
	1-21 days	4/154289	2.61	1.53 (0.42, 3.92)		0/252	0.01			
	3-5 months									
	1-7 days	0/8333	0.13			2/126496	1.9	1.05 (0.13, 3.80)		
	1-21 days	0/8333	0.39			5/126496	5.69	0.88 (0.29, 2.05)		
	5-7 months			Expected n: Expected numbers of						
	1-7 days	0/911	0.02	cases of intussusception post		0/10993	0.22			
	1-21 days	1/911	0.06	rotavirus vaccine were calculated		1/10993	0.67			
	7-9 months			by multiplying the child-time at risk						
	1-7 days	0/176	0	post-vaccination, based on the		0/688	0.01			
	1-21 days	0/176	0.01	number of children who had		1/688	0.03			
				received vaccine during the period						
				of observation, by the estimated						
				background incidence of						
				intussusceptions.						

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

RV1 Study details	Age Time after dose	Dose 1	Dose 2	What can we learn from this study?
Mexico3 RV1 **RV1 Reyna-Figueroa 2011**[27] **Country:** Mexico **Design:** Passive surveillance **Data collection:** 2008-2009 **Age:** 2-7 months	**2-7 months**	Out of 7,691,757 doses distributed there were 4 confirmed cases of intussusception up to 54 days after vaccination. Data was taken from national passive surveillance. It is compulsory by law to report serious adverse events after vaccination in Mexico. There was one case of intussusception in a 2 months old boy after the first dose.	There were three cases of intussusception after the second dose, in 4 months, 5 months and 7 months old girls.	**From this study no conclusions regarding the risk of intussusception after rotavirus vaccination can be made.** The study found four validated cases of intussusception in an unknown number of vaccinated infants corresponding to 0.029/10,000 distributed doses. There was no comparison group.
World-wide RV1 **RV1 Escolano 2011**[24] **Country:** Not specified **Design:** Case series **Data collection:** 2005-2010 **Age:** ≤1 year	**≤1 year** 0-2 days 3-7 days 8-14 days 15-30 days	111 cases of IS after RV1 administration. Median age of children was 3 months (range: 45-356 days). n 16 63 9 23	40 cases of IS after RV1 administration. Median age of children was 4.5 months (range: 87-191 days). n Ratio of Incidence Ratios (95% CI)* 8 1.57 (0.45-5.45) 11 4.97 (1.72-14.3) 8 0.42 (0.09-2.02) 13 1 *The incidence ratio calculated after administration of the first dose was divided by that calculated after the second dose.	**The incidence ratio for the period three through seven days after the first dose was five times as high as that for the same period after the second dose. No significant excess was observed during the other periods.** Analysis of spontaneously reported cases of intussusception. Unclear if the source is a GSK database.

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

RV1 Study details	Age Time after dose	Dose 1	Dose 2	What can we learn from this study?
Mexico2 RV1 **RV1 Velazquez 2010**[33] **Country:** Mexico **Design:** Active surveillance (66 hospitals) (self-control case series) **Data collection:** 2008-2009 **Age:**≤1 year	**≤1 year**	During this two-year period, there were approximately 1 million infants under surveillance; 459 IS episodes were reported in 457 children. Two subjects each had two episodes of IS reported both after the second dose. The complete observation period starts at Dose 2 and goes through one year of age. The risk period is the 31 days after Dose 2. The control period is the remainder of time through one year of age. This analysis only includes children who have received 2 doses of vaccine.[4]		**There was no statistically significant association between RV1 and intussusception after any dose.** Applying the RR observed from the interim analysis of the PASS in Mexico to estimates of background rates of IS in the US would approximate 0 to 4 additional cases of IS hospitalizations per 100,000 vaccinated infants within the 31 days after the first dose. In the first year of life, the background rate of IS hospitalizations in the US is approximately 34 per 100,000 infants.[4]
		68 IS episodes occurred after the first dose.[4] Relative incidence of IS was 1.752 (99% CI: 0.997–3.080) post-dose 1 (P = 0.010).	**77 IS episodes occurred after the second dose**.[4] Relative incidence of IS was 1.076 (99% CI: 0.618–1.873) post-dose 2 (P = 0.734).	
Singapore RV1-RV5 **RV1-RV5 Tan 2009**[51] **Only data on RV1 vaccine** **Country:** Singapore **Design:** Active surveillance (Historical control at one hospital) **Data collection:** 1997-2007 **Age:** ≤2 years		<u>Average no. IS cases per year in pre-vaccine era (1997-2005):</u>		**The study found no increase of intussusception incidence for children in Singapore after rotavirus vaccines became available (>90% RV1).**
	< 1 year	23.11/41743		
	1 to < 2 yrs	3.11/40792		
	< 2 years	26.22/82535		
		During pre-vaccine years 1997-2005 the reported incidence of IS per 100,000 was an average* of 55.98 in children aged <1 year and 31.24 in children < 2 years. *average calculated by review authors.		
		<u>Average no. IS cases per year post-vaccine era (2006-2007), vaccine cover 15-25%:</u>		
	< 1 year	12/38122		
	1 to < 2 yrs	8/38119		
	< 2 years	20/76241		
		In 2006 and 2007 the reported incidence of IS per 100,000 was 26.1 and 35.6 in children aged <1 year and 23.8 and 28.7 in children < 2 years, respectively.		

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

Table A4.5b: Cases of Intussusception with RV5

RV5 Study details	Age Time after dose	Dose 1				Dose 2				Dose 3				What can we learn from this study?
USA3 RV5 **RV5 Geier 2008, data from companion paper Haber et al. 2008**[66] **Country:** USA **Design:** Passive surveillance **Data collection:** 2006-2007 **Age:** ≤6 months		The VAERS database is a passive surveillance tool maintained jointly by the CDC and FDA, on which physicians, parents and the public report adverse events of vaccines.												**A statistically non-significant excess of observed cases compared to expected cases were reported for children aged 15-23 weeks up to 7 days after the first dose and for children aged 6-14 weeks up to 21 days after the second dose.** Total number of children vaccinated not reported. Data from VAERS, it is likely this data overlaps with RV5 Shui 2012[72] (data from VSD).
		n	Exp n	RR* (95% CI)	*P*	n	Exp n	RR* (95% CI)	*P*	n	Exp n	RR* (95% CI)	*P*	
	6-14 weeks													
	1-7 days	11	13	0.83 (0.34-2.01)	.69	1	0	13.6 (0.32-90.8)	.08	0	0			
	1-21 days	14	40	0.35 (0.15-0.81)	.012	2	0	9.10 (1.00-40.2)	.02	0	0			
	15-23 weeks													
	1-7 days	2	1	1.92 (0.22-7.74)	.30	8	17	0.46 (0.18-1.06)	.07	0	0			
	1-21 days	2	3	0.64 (0.07-2.58)	.76	18	52	0.35 (0.18-0.67)	<.001	0	0			
	24-35 weeks													
	1-7 days	0	1	0.00 (0.00-6.01)	1.00	0	2	0.00 (0.00-2.19)	.42	5	16	0.31 (0.10-0.77)	.006	
	1-21 days	0	2	0.00 (0.00-2.01)	.26	2	5	0.38 (0.04-1.45)	.23	9	49	0.18 (0.08-0.38)	<.001	
		Exp n: The expected number of background cases were calculated by multiplying the background rate of intussusception for each age group (from VSD 2000-2004) by the estimated number of vaccine doses administered (assumed to be equal to the number of doses distributed by the manufacturer) as dose 1, 2, or 3 to infants in that age group. RR*: rate ratio												
Australia3 RV1-RV5 **RV1-RV5 Buttery 2011**[36] **Only data on RV5 vaccine** **Country:** Australia **Design:** Active surveillance **Data collection:** 2007-2008 **Age:** ≤9 months		Cases (n/N)	Exp n	RR (95% CI)		Cases (n/N)	Exp n	RR (95% CI)		Cases (n/N)	Exp n			**A statistically significant excess in observed compared to expected intussusception cases was reported for children aged 1-3 months up to 7 and up to 21 days after the first dose.** 296,023 children were vaccinated with RV5 The overall RR for intussusception was 1.15 (95%CI 0.37-2.68) for 7 days and 0.77 (95%CI 0.37-1.41) for 21 days after vaccination. It is likely this data overlaps with RV1-RV5 Lawrence 2008[42] & RV1-RV5 Menzies 2009[44].
	1-3 months													
	1-7 days	3/111553	0.57	5.26 (1.09, 15.4)		0/132	0			0/9	0			
	1-21 days	6/111553	1.71	3.51 (1.29, 7.64)		0/132	0			0/9	0			
	3-5 months													
	1-7 days	0/3589	0.04			2/90441	1.5	1.33 (0.16, 4.82)		0/176	0			
	1-21 days	1/3589	0.13			3/90441	4.51	0.67 (0.14, 1.94)		0/176	0.01			
	5-7 months													
	1-7 days	0/616	0.01			0/8079	0.19			0/70994	1.71			
	1-21 days	0/616	0.04			0/8079	0.57			0/70994	0.53			
	7-9 months													
	1-7 days	0/199	0.01			0/639	0.02			0/9896	0.29			
	1-21 days	0/199	0.02			0/639	0.06			0/9896	0.88			
		Expected n: Expected numbers of cases of intussusception post rotavirus vaccine were calculated by multiplying the child-time at risk post-vaccination, based on the number of children who had received vaccine during the period of observation, by the estimated background incidence of intussusception.												

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

RV5 Study details	Age Time after dose	Dose 1	Dose 2	Dose 3	What can we learn from this study?
France RV5 **RV5 Gagneur 2011**[63] **Country:** France **Design:** Prospective cohort study (active surveillance) **Data collection:** 2007-2009 **Age:** ≤5 years		4684 infants received at least one dose of vaccine. Total number of children receiving each dose and total non-vaccinated not reported. Non-vaccinated children: 4 cases of intussusception, total not reported. No cases after the first dose.	1 case after the second dose, 13 days after vaccination, aged 14 weeks.	1 case after the third dose, 14 days after vaccination, aged 21 weeks.	**From this study no conclusions regarding the risk of intussusception after rotavirus vaccination can be made.** The study found four validated cases of intussusception in an unknown number of unvaccinated infants and two cases in 4684 RV5 vaccinated infants, neither case occurred after the first dose.
USA13 RV5 **RV5 Shui 2012**[72] **Country:** USA **Design:** Prospective cohort study and historical control **Data collection:** 2006-2010 **Age:** 4-34 weeks		IS following RV5 vaccine vs. IS following other vaccines:			**There were no statistically significant increased risks of intussusception in either the 1- to 30-day window or the 1- to 7-day risk window for all doses combined or in dose-specific analyses after adjusting for age.** Data from VSD, it is likely this data overlaps with Haber et al. 2008[66] (data from VAERS).
		RV5 Cases/309,844 doses / Other vacc cases/102,523 doses / RR (95% CI)	RV5 Cases/257,915 doses / Other vacc cases/114,385 doses / RR (95% CI)	RV5 Cases/218,966 doses / Other vacc cases/172,118 doses / RR (95% CI)	
	1-7 days	1 / 0 / Undefined	0 / 1 / 0 (0.0-17.3)	2 / 1 / 1.57 (0.08-92.75)	
	1-30 days	4 / 0 / Undefined	4 / 5 / 0.36 (0.07-1.65)	6 / 3 / 1.57 (0.34-9.72)	
		ICD-9 codes for IS following RV5 vaccination (2006-2010) vs historical unexposed rates (2001-2005):			
		Obs / Exp / No. Doses / SIR (95% CI)	Obs / Exp / No. Doses / SIR (95% CI)	Obs / Exp / No. Doses / SIR (95% CI)	
	1-7 days	1 / 0.8 / 309,844 / 1.21 (0.03-6.75)	1 / 1.6 / 257,915 / 0.62 (0.13-3.80)	2 / 1.9 / 218,966 / 1.05 (0.25-2.36)	
	1-30 days	7 / 5.7 / 309,844 / 1.23 (0.50-2.54)	7 / 7.2 / 257,915 / 0.97 (0.39-2.00)	7 / 8 / 218,966 / 0.88 (0.35-1.81)	
		Exp: Expected cases of intussusception were based on background rates from VSD 2001-2005 (ICD-9 codes) stratified by age and care site. SIR: Standardized Incidence Ratio, computed by dividing the number of observed visits for intussusceptions following RV5 by the number of expected visits.			

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

Table A4.5c: Cases of intussusception with licensed rotavirus vaccines

RV1 and RV5 combined Study details	Results	What can we learn from this study?
Germany2 RV1-RV5 **RV1-RV5 Jenke 2001**[41] **Country:** Germany **Design:** Active surveillance **Data collection:** 2006-2007 **Age:** ≤15 years	319 hospitals in Germany reports to the German Paediatric Surveillance Unit (ESPED) on a monthly basis. This database was searched for reported cases of intussusception. 1200 definite IS cases were reported, five of the reported cases occurred after rotavirus vaccination, three of them in children ≥6 months.	**From this study no conclusions regarding the risk of intussusception after rotavirus vaccination can be made. However, three of the five vaccinated children with intussusception were vaccinated above the recommended age.** Dose, time after vaccination, total number of children vaccinated and ages of children not reported.
Australia1 RV1-RV5 **RV1-RV5 Lawrence 2008**[42] **Country:** Australia **Design:** Passive surveillance **Data collection:**2007 **Age:**≤7 years	Australian passive surveillance data for adverse events following immunisation (AEFI) reported to the Therapeutic Goods Administration (TGA) for from July to December 2007 (the period where the vaccine was included in the funded National Immunisation Program schedule): • 3 reports of intussusception (1.4 per 100,000 administered doses) occurring 6, 16, and 31 days after vaccination.	**From this study no conclusions regarding the risk of intussusception after rotavirus vaccination can be made.** Control group, dose, total number of children vaccinated and ages of children not reported. It is likely this data overlaps with RV1-RV5 Buttery 2011[36].
Australia4 RV1-RV5 **RV1-RV5 Mahajan 2011**[43] **Country:** Australia **Design:** Passive surveillance **Data collection:** 2010 **Age:** ≤7 years	Australian passive surveillance data for AEFI reported to the TGA for 2010: • 1 case of IS, occurred 2 months after administration of hexavalent (DTPa IPV-HepB-Hib), pneumococcal (PCV7) and rotavirus vaccines. However, due to the length of latency, causality is unlikely to be related to the vaccine.	**From this study no conclusions regarding the risk of intussusception after rotavirus vaccination can be made.** Control group, dose, total number of children vaccinated and ages of children not reported.

Australia2 RV1-RV5
 	
RV1-RV5 Menzies 2009[44]
 	
Country: Australia
Design: Passive surveillance
Data collection: 2008
Age: ≤7 years
	Australian passive surveillance data for AEFI reported to the TGA for 2008:
	• 14 reports of intussusception (2.7 per 100,000 administered doses).
	  ○ Ten were in children aged 2 to 3 months, and four aged 4 to 5 months.
	  ○ Ten of the cases occurred within 30 days of receiving a dose of the vaccine.
	  ○ The majority (10/14) of intussusception reports were infants after dose 1 (2–3 months age group) and 4 cases after dose 2 (4–5 months age group).
		From this study no conclusions regarding the risk of intussusception after rotavirus vaccination can be made.
		
		Control group, dose, time after vaccination and total number of children vaccinated not reported.
		
		It is likely this data overlaps with RV1-RV5 Buttery 2011[36].

AE=adverse event; AEFI=adverse events following immunisation; CDC= Centers for Disease Control and Prevention; CI=confidence interval; FDA=Food and Drug Administration; ICD-9= International Classification of Diseases, Ninth Revision; IR=incidence ratio; IS=intussusception; nr=not reported; OR=odds ratio; RR=risk ratio; RR*= rate ratio; RV=rotavirus; RVGE rotavirus gastroenteritis; SAE=serious adverse event; SIR=standardized incidence ratio; SCID=severe combined immunodeficiency; TGA=Therapeutic Goods Administration; VAERS=Vaccine Adverse Events Reporting System; VSD=vaccine safety datalink

Appendix 5: RV1 and RV5 effectiveness against severe rotavirus diarrhoea or rotavirus diarrhoea related health care encounters caused by different serotypes

RV1 is derived from the G1P[8] serotype and RV5 from G1, G2, G3, G4 and P1A[8] serotypes. Some trials and observational studies have tried to ascertain whether the vaccines protect against different serotypes, both dominating and emerging, circulating in different parts of the world. The recently published Cochrane review on RCTs reported subgroup analyses on the impact of rotavirus vaccines on different serotypes, but limited information was available from RCTs. Here we summarise this information and supplement it with data from observational studies.

Results

RV1

Randomised controlled trials: Six trials reported on **severe rotavirus diarrhoea** for different G-types as subgroup analyses.[9] In all these trials only the children that had rotavirus diarrhoea were tested for serotypes. RV1 was efficacious for G1, G2 and G9. However, in two studies, one in Hong Kong, Taiwan and Singapore, and one in Singapore, there was no statistically significant efficacy for G3 and for G4, respectively. See Figure A5.1 below.

Observational studies: Six studies[16 18 19 25 32 34] reported data on **rotavirus diarrhoea related health care encounters** for different G-types as subgroup analyses comparing RV1 vaccinated and unvaccinated children ≤ 3 years old (Figure A5.2 and Table A5.1). Four studies were conducted in Brazil, one in Australia and one in Mexico. One study conducted in Brazil reported on G1, G3 and G4 but no statistically significant difference was found for any of those G-types.[16] All six studies reported on G2, and pooled results showed a statistically significant reduction with RV1, one study could not be pooled[18]. One study that was pooled reported on G2 as primary analysis and reported 77% efficacy against G2 for 6-11 months old children, and no significant effect for children > 12 months old in Brazil.[19] Two studies conducted in Brazil and Mexico reported on G9[16 34], pooled results showed no statistically significant difference. One of the studies reported on G9 as primary analysis and found 93% efficacy against G9 for 5-24 months old children in Mexico.[34] Two studies pooled all non-G2 types[25 32], pooled results showed no statistically significant difference, but with large heterogeneity.

RV5

Randomised controlled trials: One trial reported on **severe rotavirus diarrhoea** for different G-types as a subgroup analysis.[9] Only the children that had rotavirus diarrhoea were tested for serotypes. RV5 was efficacious for G1, G3, G4 and G9, but not for G2 See Figure A5.3 below.

Observational studies: Six studies[39 54 56 58 68 77] reported data on **rotavirus diarrhoea related health care encounters** for different G-types as subgroup analyses comparing RV5 vaccinated and unvaccinated children. Three out of the four studies that could be pooled were carried out in the USA and one in Nicaragua; all children were ≤ 5 years old. Pooled results showed a statistically significant efficacy for G2 with RV5. Pooled results for G1, G3, G4, G8, G9 and G12 found no statistically significant efficacy and large heterogeneity (Figure A5.4 below).

Two studies could not be pooled. One of them, conducted in the USA with children ≤ 2 years old, found 95% efficacy against G3 and 92% efficacy against non-G3 serotypes.[13] From the other study, conducted in Nicaragua, no conclusions could be made due to small sample size.[20] See Table A5.1.

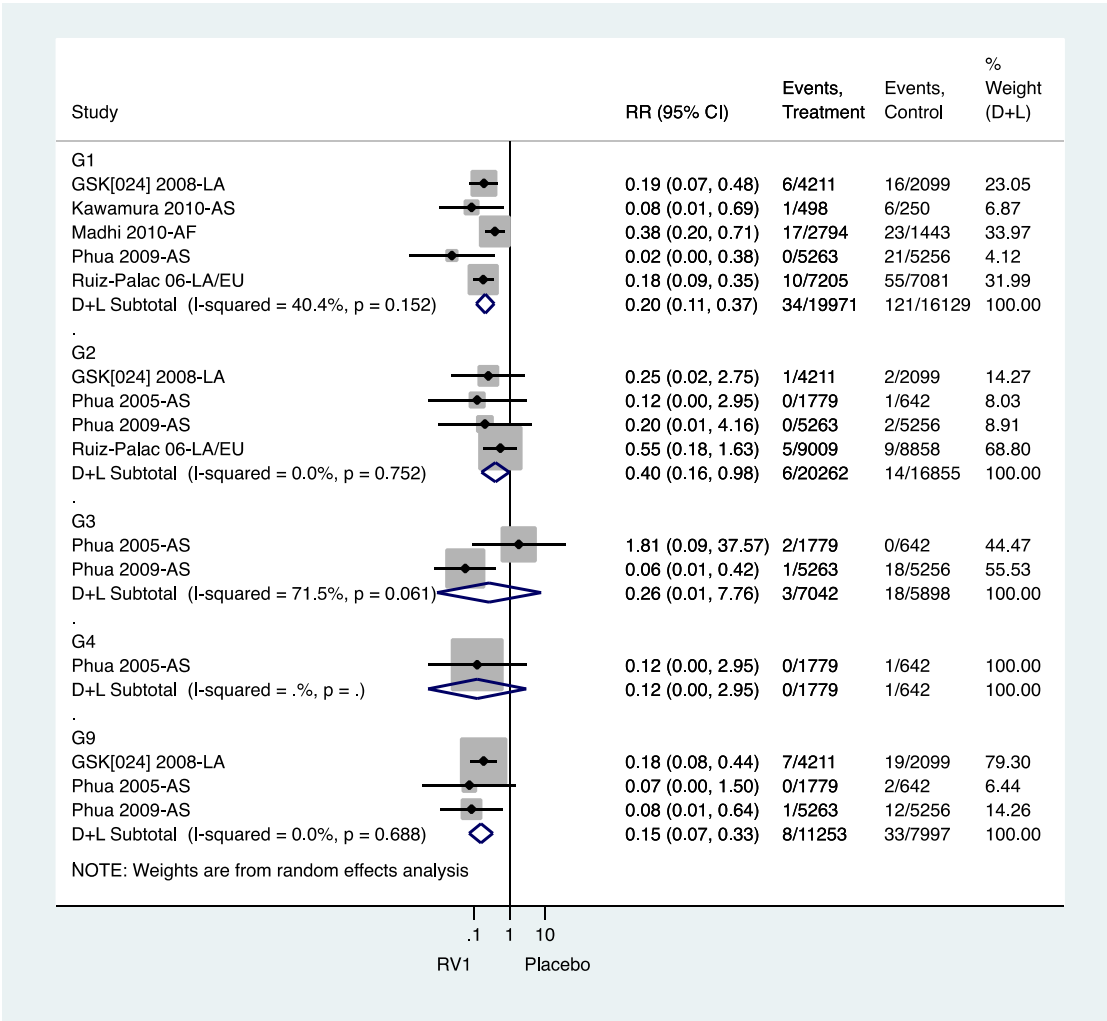
RV1/RV5

Two observational studies[38 52] reported data on **rotavirus diarrhoea related health care encounters** for different G-types comparing RV1 or RV5 vaccinated and unvaccinated children. No conclusions could be made, due mainly to low sample sizes. See Table A5.1.

Conclusions

There is no evidence that rotavirus vaccines are more efficacious in some but not other serotypes.

Figure A5.1: Severe rotavirus diarrhoea caused by different serotypes from RCTs comparing RV1 to placebo



| Data extracted from Soares-Weiser et al (2012) Cochrane review[9] |

Figure A5.2: Rotavirus diarrhoea related health care encounters caused by different serotypes from observational studies comparing RV1 vaccinated to unvaccinated children

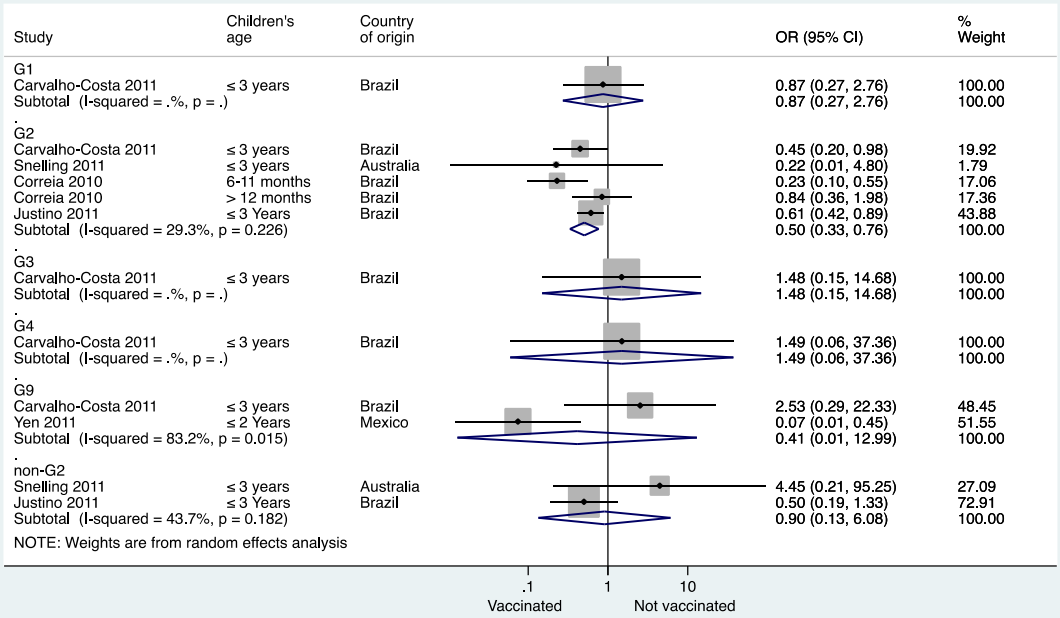
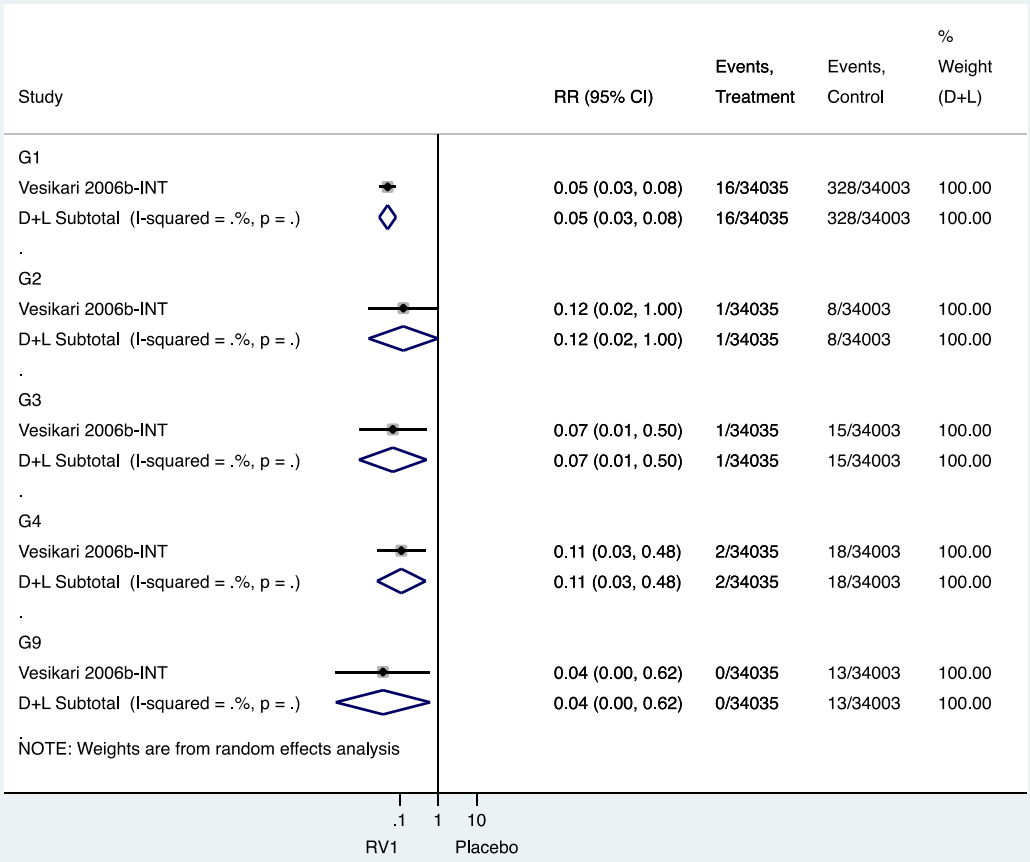


Figure A5.3: Severe rotavirus diarrhoea caused by different serotypes from RCTs comparing RV5 to placebo



| Data extracted from Soares-Weiser et al (2012) Cochrane review[9] |

Figure A5.4: Rotavirus diarrhoea related health care encounters caused by different serotypes from observational studies comparing RV5 vaccinated to unvaccinated children

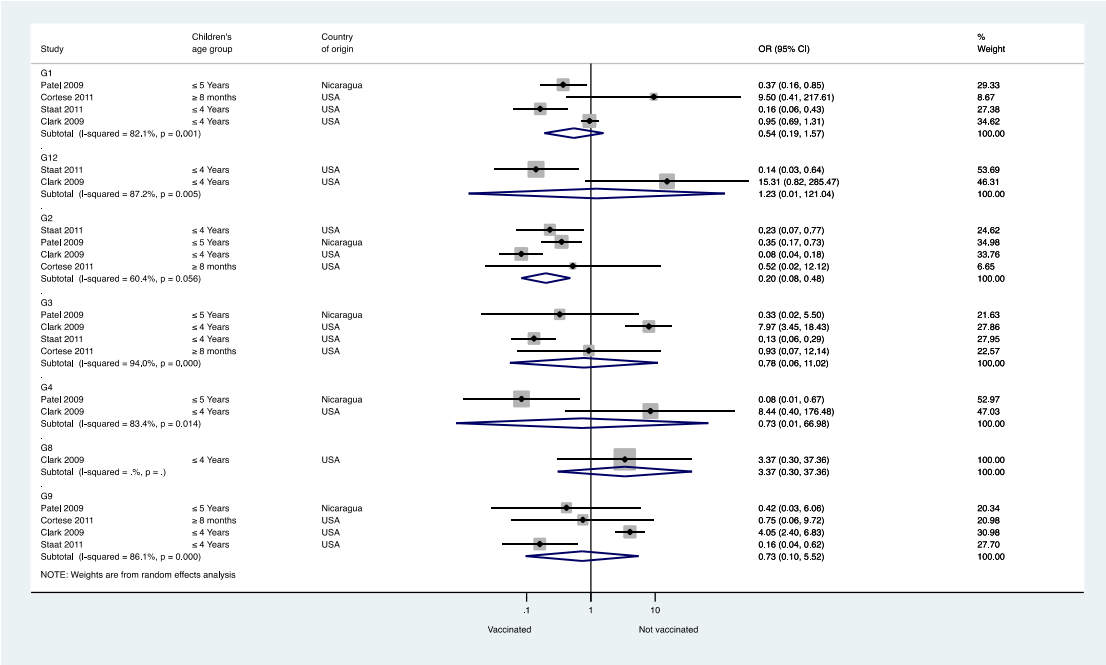


Table A5.1: Narrative results of studies evaluating RV1 and RV5 vaccine efficacy[3] against different rotavirus G-serotypes

<table>
<tr><th>Study</th><th>Results</th><th>What can we learn from this study?</th></tr>
<tr><td>Brazil3 RV1
RV1 Carvalho-Costa 2011[16]

Country: Brazil
Design: Surveillance study
Data collection: Jan 2005 – Dec 2009
Age: “eligible to receive rotavirus vaccine”</td><td>
<table>
<tr><th></th><th>G1 (%)</th><th>G2 (%)</th><th>G3 (%)</th><th>G4 (%)</th><th>G9 (%)</th></tr>
<tr><td>Vaccinated (N=90)*</td><td>9 (10)</td><td>49 (54.4)</td><td>3 (3.3)</td><td>1 (1.1)</td><td>5 (5.5)</td></tr>
<tr><td>Unvaccinated (N=44)**</td><td>5 (11.4)</td><td>32 (72.7)</td><td>1 (2.3)</td><td>0</td><td>1 (2.3)</td></tr>
</table>
*90/539 fully vaccinated children tested positive for RVGE
**44/178 unvaccinated, age eligible children tested negative for RVGE
</td><td>A larger proportion of unvaccinated children were infected with the G2 serotype, and a larger proportion of vaccinated children were infected with the G9 serotype, compared to children in the other vaccine group, but no analysis was reported for this outcome.</td></tr>
<tr><td>Brazil2 RV1
RV1 Correia 2010[19]

Country: Brazil
Design: Case control study
Data collection: Mar 2006 – Sep 2008
Age: 6 – 33 months</td><td>
<table>
<tr><th>Group*</th><th>Age</th><th>N</th><th>n vaccinated (%)</th><th>VE (95% CI)**</th></tr>
<tr><td>Cases</td><td>6-11 months</td><td>22</td><td>12 (54)</td><td>-</td></tr>
<tr><td>RV negative controls</td><td>6-11 months</td><td>183</td><td>131 (72)</td><td>77% (42 to 91%)</td></tr>
<tr><td>ARI controls</td><td>6-11 months</td><td>83</td><td>70 (84)</td><td>77% (43 to 90%)</td></tr>
<tr><td>Cases</td><td>>12 months</td><td>39</td><td>31 (80)</td><td>-</td></tr>
<tr><td>RV negative controls</td><td>>12 months</td><td>241</td><td>196 (77)</td><td>-24% (-190 to 47%)</td></tr>
<tr><td>ARI controls</td><td>>12 months</td><td>288</td><td>240 (83)</td><td>15% (-101 to 64%)</td></tr>
</table>
*Cases: children at hospital with severe diarrhoea where rotavirus G2P[4] was detected; RV negative controls: children at hospital with severe diarrhoea that tested negative for rotavirus; ARI controls: children at hospital with acute respiratory infection.
**VE calculated from the adjusted odds ratio (month and year of birth): (1-OR)x100
</td><td>This study reported primarily on G2 rotavirus related health care encounters.

Statistically significant efficacy against rotavirus diarrhoea of the G2P[4] type, a serotype not included in the RV1 vaccine, was 77% for children 6-11 months old. There was no statistically significant vaccine effect for children > 12 months.</td></tr>
<tr><td>Brazil1 RV1
RV1 Gurgel 2009[18]

Country: Brazil
Design: Surveillance study
Data collection: Oct 2006 – April 2008
Age: < 10 years</td><td>The vaccine efficacy* against G2P[4] among children hospitalized with acute rotavirus diarrhoea was 89% (95% CI: 87% - 92%)** in Aracaju and 95% in Sergipe state.

*VE=(PPV – PCV) / PPV (1 – PCV), PPV: proportion of RV cases vaccinated, PCV: proportion of population vaccinated
**reported in paper “89% (95% CI: 0.87% - 0.92%)”, we assume CI is a typo.</td><td>Efficacy against rotavirus diarrhoea of the G2P[4] type, a serotype not included in the RV1 vaccine, was 89% and statistically significant.</td></tr>
</table>

[3] Efficacy as defined by each study.

ARI=acute respiratory infection; CI= confidence interval; n= number of cases; N=total number of children; PCV=Proportion of cases vaccinated; PPV=Proportion of population vaccinated; RV=rotavirus; RVGE= rotavirus gastroenteritis; VE=vaccine efficacy

<table>
<tr><th>Study</th><th>Results</th><th>What can we learn from this study?</th></tr>
<tr>
<td>Brazil5 RV1
RV1 Justino 2011[25]

Country: Brazil
Design: Case control study
Data collection: May 2008 – May 2009
Age: 3 – 36 months</td>
<td>
<table>
<tr><th></th><th colspan="2">G2P[4]</th><th colspan="2">Pooled non- G2P[4]</th></tr>
<tr><th>Group*</th><th>N</th><th>VE (95% CI)**</th><th>N</th><th>VE (95% CI)**</th></tr>
<tr><td>Hospital controls</td><td>286</td><td>38.9 (11.1 to 58.0)</td><td>46</td><td>50.0 (-33.2 to 81.2)</td></tr>
<tr><td>Neighbourhood controls</td><td>222</td><td>75.4 (56.7 to 86.0)</td><td>42</td><td>70.0 (-9.0 to 91.7)</td></tr>
</table>
*Cases: children hospitalized with RVGE; Hospital controls: date of birth matched children hospitalized for other reasons than diarrhoea; Neighbourhood controls: date of birth matched children without diarrhoea residing in the same neighbourhood as the case.
** vaccine efficacy ((1-matched OR) x100) compared to matched cases
</td>
<td>This study reported primarily on G2 rotavirus related health care encounters.

Efficacy against rotavirus diarrhoea of the G2P[4] type, a serotype not included in the RV1 vaccine, was 39-75% and statistically significant. There was no statistically significant vaccine efficacy for pooled non-G2P[4] types.</td>
</tr>
<tr>
<td>Australia2 RV1
RV1 Snelling 2011[32]

Country: Australia
Design: Case control study
Data collection: Sep 2008 – Jun 2009
Age: 6 weeks - 36 months</td>
<td>
<table>
<tr><th></th><th>G2P[4]</th><th>Non G2P[4]</th><th>Non-typable</th></tr>
<tr><td>Fully vaccinated (N*=19)</td><td>15</td><td>1</td><td>3</td></tr>
<tr><td>Unvaccinated (N*=10)</td><td>10</td><td>0</td><td>0</td></tr>
</table>
*N=number of cases referred for genotyping
</td>
<td>This study reported primarily on G2 rotavirus related health care encounters.

From this study no conclusions can be made in relation to the effect of RV1 on rotavirus diarrhoea of different G-serotypes.

Few cases were referred for genotyping and no analysis was reported for this outcome.</td>
</tr>
<tr>
<td>Mexico4 RV1
RV1 Yen 2011[34]

Country: Mexico
Design: Case control study
Data collection: March 2010 – May 2010
Age: 5 months – 2 years</td>
<td>Effectiveness* of a complete 2 dose series of RV1 against G9P[4] rotavirus infection resulting in hospitalization was 94% (95% CI: 16-100%, p-value=0.03).

*Vaccine effectiveness: (1-OR)x100; OR for vaccination of cases (children hospitalized with acute G9P[4] RVGE) vs. controls (matched for date of birth and reside in the same municipality as the case)</td>
<td>This study reported primarily on G9 rotavirus related health care encounters.

Efficacy against rotavirus diarrhoea of the G9P[4] type, a serotype not included in the RV1 vaccine, was 94% and statistically significant.</td>
</tr>
<tr>
<td>Nicaragua3 RV5
RV5 Becker-Dreps 2011b[54]

Country: Nicaragua
Design: Surveillance study
Data collection: Apr 2008 – Mar 2009
Age: 10 weeks – 36 months</td>
<td>14/403 stool samples collected from children visiting primary care clinics tested positive for rotavirus. One child with a mixed infection was unvaccinated, three children were partially vaccinated and 10 were fully vaccinated. G-types of samples were as follows:
<table>
<tr><th></th><th>G1P[8]</th><th>G2P[4]</th><th>G3P[8]</th><th>G4P[6]</th><th>Others*</th></tr>
<tr><td>Vaccinated (N=11)</td><td>4</td><td>2</td><td>1</td><td>1</td><td>3</td></tr>
<tr><td>Unvaccinated (N=3)</td><td>0</td><td>0</td><td>0</td><td>0</td><td>3</td></tr>
</table>
*Mixed infections, untyped or untypable
</td>
<td>From this study no conclusions can be made in relation to the effect of RV1 on rotavirus diarrhoea of different G-serotypes.

Few children tested positive for rotavirus and no analysis was reported for this outcome.</td>
</tr>
</table>

ARI=acute respiratory infection; CI= confidence interval; n= number of cases; N=total number of children; PCV=Proportion of cases vaccinated; PPV=Proportion of population vaccinated; RV=rotavirus; RVGE= rotavirus gastroenteritis; VE=vaccine efficacy

<table>
<tr><th>Study</th><th>Results</th><th>What can we learn from this study?</th></tr>
<tr>
<td>USA7 RV5
RV5 Boom 2010[56]

Country: USA
Design: Case control study
Data collection: Feb 2008 – Jun 2009
Age: 15 days – 23 months</td>
<td>
<table>
<tr><th>Group*</th><th>G3P[8]
VE (95% CI)**</th><th>non-G3P[8]
VE (95% CI)**</th></tr>
<tr><td>RV negative controls</td><td>95% (60-99%)</td><td>93% (41-99%)</td></tr>
<tr><td>ARI controls</td><td>95% (27-100%)</td><td>91% (29-99%)</td></tr>
<tr><td>Combined control groups</td><td>95% (57-99%)</td><td>92% (40-99%)</td></tr>
</table>
*Compared to cases: children at hospital with severe RV positive diarrhoea; RV negative controls: children at hospital with severe diarrhoea that tested negative for rotavirus; ARI controls: children at hospital with acute respiratory infection.
**VE=(1-OR)x100, compared to matched cases
</td>
<td>This study reported primarily on G3 rotavirus related health care encounters.

Efficacy against rotavirus diarrhoea of theG3 type, a serotype included in the RV5 vaccine, was 95% and statistically significant. Efficacy against pooled non-G3 types was 92% and statistically significant.</td>
</tr>
<tr>
<td>USA4 RV5
RV5 Clark 2009[58]

Country: USA
Design: Surveillance study with historical control
Data collection: Dec 2005 – Jun 2009
Age: not reported</td>
<td>
<table>
<tr><th>Era*</th><th>G1 (%)#</th><th>G2 (%)#</th><th>G3 (%)#</th><th>G4 (%)#</th><th>G8 (%)#</th><th>G9 (%)#</th><th>G12 (%)#</th></tr>
<tr><td>Pre-vaccine (N=446)</td><td>295 (66.1)</td><td>110 (24.7)</td><td>7 (1.6)</td><td>0 (0)</td><td>1 (0.2)</td><td>23 (5.2)</td><td>10 (2.2)</td></tr>
<tr><td>Post-vaccine (N=266)</td><td>173 (65)</td><td>7 (2.6)</td><td>30 (11.3)</td><td>2 (0.8)</td><td>2 (0.8)</td><td>48 (18)</td><td>4 (1.5)</td></tr>
</table>
N=number of children at hospital with RVGE
*Pre-vaccine era: 04/05 and 05/06 seasons; post-vaccine era: 06/07, 07/08 and 08/09 rotavirus seasons, coverage: 50% nation-wide by 2007, estimated 60% in Philadelphia (where the study was carried out) mid-2008 .
#% calculated by review authors
</td>
<td>A larger proportion of children were infected with the G3 and G9 serotypes in the post-vaccine era compared to the pre-vaccine era, and a larger proportion were infected with the G2 serotype in the pre-vaccine era compared to the post-vaccine era, but no analysis was reported for this outcome.</td>
</tr>
<tr>
<td>USA9 RV5
RV5 Cortese 2011[39]

Country: USA
Design: Case control study
Data collection: Dec 2006 – Jun 2009
Age: children > 8 weeks</td>
<td>
<table>
<tr><th></th><th>G1P[8]</th><th>G2P[4]</th><th>G3P[8]</th><th>G9P[8]</th><th>G12P[8]</th></tr>
<tr><td>Fully vaccinated cases* (N=3)</td><td>0</td><td>0</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Unvaccinated cases* (N=20)</td><td>1</td><td>4</td><td>7</td><td>8</td><td>0</td></tr>
</table>
*Cases were children at hospital with RV confirmed diarrhoea.
</td>
<td>From this study no conclusions can be made in relation to the effect of RV1 on rotavirus diarrhoea of different G-serotypes.

Rotavirus serotypes were only reported for two locations during one season, and no analysis was reported for this outcome.</td>
</tr>
<tr>
<td>Nicaragua1 RV5
RV5 Patel 2009[68]

Country: Nicaragua
Design: Surveillance study
Data collection: Jun 2007 – Jun 2008
Age: ≤ 2 years</td>
<td>Strain characterization was conducted on 262 RV positive diarrhoea patients:
• 231 (80%) were G2P[4],
• 14 (5%) were G1P[8],
• the remaining were uncommon or mixed strains (15%).
For G2P[4] RV5 vaccination was associated with a reduction in rotavirus disease requiring admission or intravenous hydration (adjusted OR: 0.49, 95% CI: 0.31-0.77).</td>
<td>Efficacy against rotavirus diarrhoea of theG2 type, a serotype included in the RV5 vaccine, was 51% and statistically significant.</td>
</tr>
</table>

ARI=acute respiratory infection; CI= confidence interval; n= number of cases; N=total number of children; PCV=Proportion of cases vaccinated; PPV=Proportion of population vaccinated; RV=rotavirus; RVGE= rotavirus gastroenteritis; VE=vaccine efficacy

<table>
<tr><th>Study</th><th>Results</th><th>What can we learn from this study?</th></tr>
<tr>
<td>USA12 RV5
RV5 Staat 2011[77]

Country: USA
Design: Case control study
Data collection: Jan 2006 – Jun 2009
Age: 15 days – 47 months</td>
<td>
<table>
<tr><th></th><th></th><th colspan="2">Cases vs. RV negative control group analysis</th><th colspan="2">Cases vs. ARI control group analysis</th></tr>
<tr><th>G-type</th><th>Group*</th><th>n/N (%)</th><th>% VE# (95% CI)</th><th>n/N (%)</th><th>% VE# (95% CI)</th></tr>
<tr><td>G1</td><td>cases
controls</td><td>5/39 (13)
53/100 (53)</td><td>96 (79 to 99)</td><td>5/44 (11)
74/168 (44)</td><td>88 (60 to 97)</td></tr>
<tr><td>G2</td><td>cases
controls</td><td>4/27 (15)
20/50 (40)</td><td>72 (-7 to 92)</td><td>4/29 (14)
68/120 (57)</td><td>77 (22 to 93)</td></tr>
<tr><td>G3</td><td>cases
controls</td><td>12/44 (27)
68/101 (67)</td><td>86 (60 to 95)</td><td>13/51 (25)
126/198 (64)</td><td>87 (71 to 94)</td></tr>
<tr><td>G9</td><td>cases
controls</td><td>8/24 (33)
26/40 (65)</td><td>83 (17 to 97)</td><td>9/29 (31)
59/84 (70)</td><td>84 (40 to 96)</td></tr>
<tr><td>G12</td><td>cases
controls</td><td>3/21 (14)
11/29 (38)</td><td>90 (4 to 99)</td><td>3/25 (12)
31/85 (36)</td><td>86 (37 to 97)</td></tr>
<tr><td>G1-4</td><td>cases
controls</td><td>21/111 (19)
141/255 (55)</td><td>87 (71 to 94)</td><td>22/125 (18)
268/491 (55)</td><td>85 (74 to 92)</td></tr>
<tr><td>G1-4, G9, G12</td><td>cases
controls</td><td>32/155 (21)
178/320 (56)</td><td>84 (71 to 91)</td><td>34/178 (19)
358/655 (55)</td><td>83 (73 to 89)</td></tr>
</table>
*Cases: children at hospital or ED with RV positive diarrhoea; RV negative controls: children, matched for date of birth and symptom onset date, at hospital or ED with diarrhoea that tested negative for rotavirus; ARI controls: children, matched for date of birth and symptom onset date, at hospital or ED with acute respiratory infection.
#VE= (1 - OR) x 100, where OR was a comparison of vaccination rates among cases and controls
</td>
<td>A 77-96% statistically significant vaccine efficacy was found against G1, G3, G9 and G12 serotypes, and for G2 with one of the control groups (ARI). In the analysis with the other control group (RV negative diarrhoea), no statistical significance was found for G2.

G1-3 are part of the RV5 vaccine, G9 and G12 are not.</td>
</tr>
<tr>
<td>USA2 RV1-RV5
RV1-RV5 Desai 2010[38]

Country: USA
Design: Case control study
Data collection: Jan 2008 – Aug 2009
Age: 8 weeks – 3 years</td>
<td>Among 42 cases of hospitalised, rotavirus infected children enrolled in the study, three were vaccinated with RV5 and two with RV1.
Strain typing was performed on 19 of the samples: 2 were G1 (10.5%), 1 was G2 (5.3%), 5 were G3 (26.3%), 1 was G4 (5.3%), 2 were G9 (10.5%), the rest were non-G type or not typable. Of the 5 stool samples from cases who had received vaccine, 3 had typable results. One child who had received 2 doses of RV5 was G3 positive (included in the vaccine). Another child who received 1 dose of RV5 was G9 positive (not included in the vaccine). The third child had received a full course of RV1 and was G9 positive (not included in vaccine).</td>
<td>From this study no conclusions can be made in relation to rotavirus vaccine efficacy against rotavirus diarrhoea of different G-types.

Strain characterization was performed on a very limited sample size.</td>
</tr>
<tr>
<td>Greece RV1-RV5
RV1-RV5 Trimis 2011[52]

Country: Greece
Design: Surveillance study
Data collection: Sep 2006 – Aug 2010
Age: <5 years</td>
<td>342/2589 children hospitalised with acute gastroenteritis tested positive for rotavirus. No child with RVGE had received any RV1 or RV5 vaccine dose. Both vaccines were available in Greece since Jan 2007, the national coverage 2009-2010 was below 30%.
90/147 RV positive samples 2008-10 were genotyped:
<table>
<tr><th></th><th>G1P[8]</th><th>G2P[4]</th><th>G4P[8]</th><th>G4P[4]</th><th>G9 P[8]</th><th>Mixed</th></tr>
<tr><td>2008-2009 (n=48)</td><td>8%</td><td>4%</td><td>78%</td><td>2%</td><td>2%</td><td>6%</td></tr>
<tr><td>2009-2010 (n=42)</td><td>14%</td><td>7%</td><td>65%</td><td>0%</td><td>2%</td><td>12%</td></tr>
</table>
</td>
<td>From this study no conclusions can be made in relation to rotavirus vaccine efficacy against rotavirus diarrhoea of different G-types.

None of the children hospitalized with rotavirus positive diarrhoea had received rotavirus vaccine.</td>
</tr>
</table>

ARI=acute respiratory infection; CI= confidence interval; n= number of cases; N=total number of children; PCV=Proportion of cases vaccinated; PPV=Proportion of population vaccinated; RV=rotavirus; RVGE= rotavirus gastroenteritis; VE=vaccine efficacy

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