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

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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