EXPANDING THE POTENTIAL OF ROTAVIRUS VACCINES (RV) TO REDUCE MORTALITY BY OPTIMIZING THE IMMUNIZATION SCHEDULES

POLICY QUESTIONS

What are the optimal immunization schedules for rotavirus vaccines (RV) for children living in different WHO mortality strata[1]?

1. What rotavirus vaccine schedules does the evidence favours for children living in different WHO mortality strata?
2. What evidence is available on the benefits and risks of the current and alternative RV immunization schedules for children living in different WHO mortality strata?

OVERALL CONCLUSIONS

Both rotavirus vaccines are efficacious but, data show that they are more efficacious in low mortality under five mortality settings (VE ~ 90%) than in high mortality under five settings (VE ~ 60%). Observational studies have reported similar findings.

A review estimated that the median age at infection for rotavirus for all the studies was 43.5 weeks (inter-quartile range 38 to 52 weeks). This review reported that of all the cases of rotavirus diarrhoea in children less than 3 years old that are severe enough for hospital admission, about 3% will occur before the child is 9 weeks old. About 6% will occur before 13 weeks, about 10% before 17 weeks, and 32% before they are 32 weeks old. Ideally vaccination schedules should be designed to provide benefits to those at highest risk. This might imply extending the evidence base to age distributions for different socio-economic groups.

Currently, there is limited 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. Most RCTs lack precision to examine the impact of RV1 and RV5 on intussusception with different schedules. Despite there are thirteen observational studies reporting on specific surveillance for intussusception, 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. Studies were performed mainly in countries on strata A and B.

Trade-offs exists when considering various rotavirus vaccine schedule options. On the benefits side, unrestricted schedule would prevent additional 48,400 rotavirus deaths due to ~23-25% increase in vaccine coverage. On the risks side, the unrestricted schedule is estimated to cause ~333 excess intussusception deaths compared to current age restricted schedule.

! THIS SUMMARY INCLUDES

KEY MESSAGES

EVIDENCE SUMMARIES

X THIS SUMMARY DOES NOT INCLUDE DETAILED OPERATIONAL ISSUES

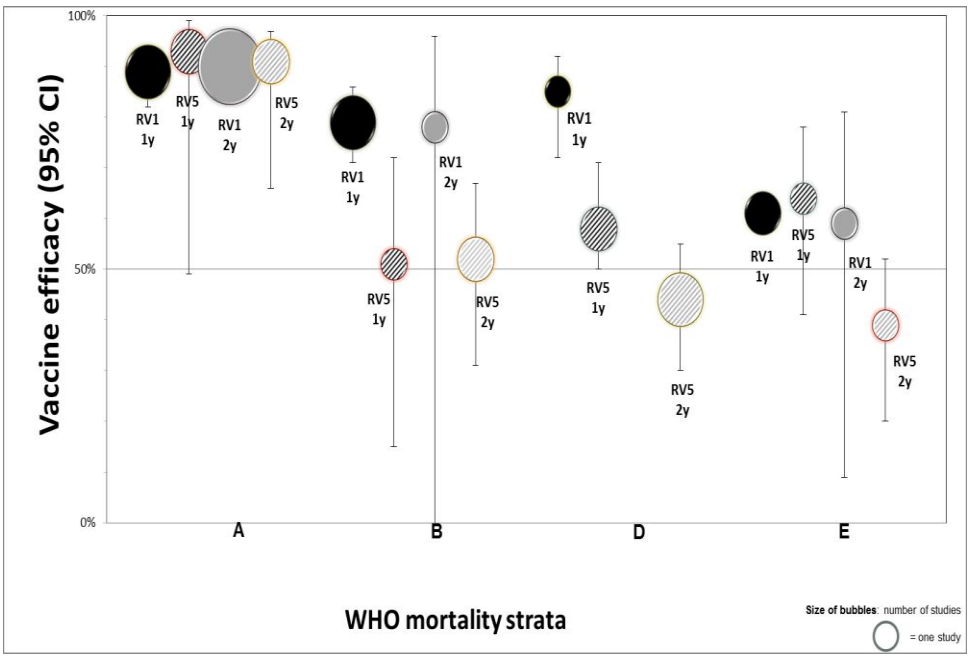
Recent reviews on the subject by the WHO Immunization Practices Advisory Committee (IPAC) committee can be found at http://www.who.int/entity/immunization_delivery/systems_policy/IPAC_2011_September_report.pdf

[1] To aid in cause of death and burden of disease analyses, the Member States of the World Health Organization (WHO) have been divided into five mortality strata on the basis of their levels of mortality of children under five years of age (5q0) and of males 15–59 years old (45q15). http://www.google.com/url?sa=t&rct=j&q=mortality%20strata%20definition&source=web&cd=1&ved=0CCAQFjAA&url=http%3A%2F%2Fwww.who.int%2Fentity%2Fmental_health%2Fneurology%2Fannexes_neuro_disorders_public_h_challenges.pdf&ei=JClvT7ufMcOSOtu_-P0F&usg=AFQjCNG3Q-ktfm8rryp2CH3mp_ZedS7cUg

KEY POLICY MESSAGES

EFFICACY AND EFFECTIVENESS[2]

Rotavirus vaccine efficacy on Severe Rotavirus Gastro-Enteritis is lower in populations with higher mortality rates in children under five years of age (WHO mortality stratum E and D)

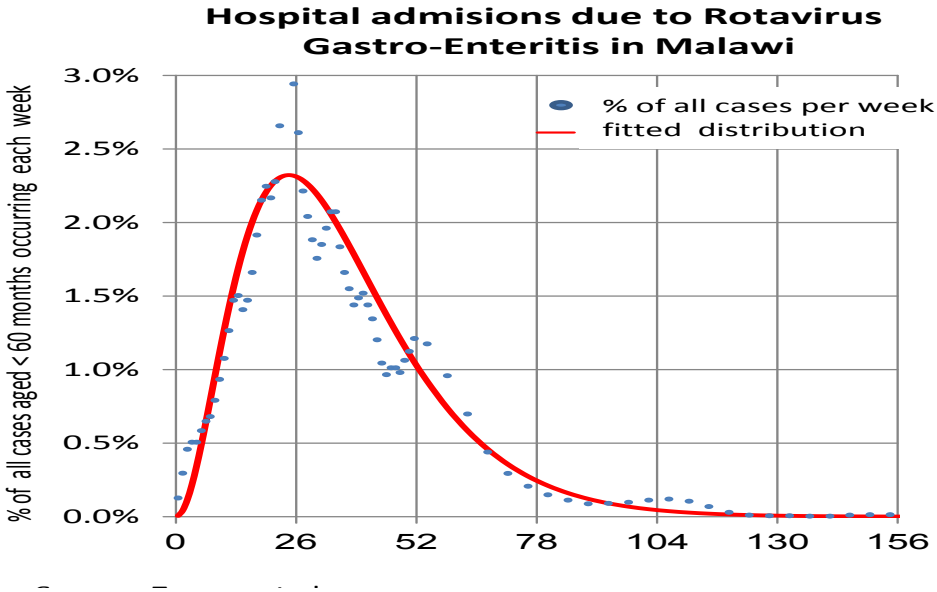


Both rotavirus vaccines are efficacious but, data show that they are more efficacious in low mortality under five mortality settings (VE ~ 90%) than in high mortality under five settings (VE ~ 60%). Observational studies have reported similar findings.

[To read more about this subject go to page 4]

EPIDEMIOLOGY, COVERAGE AND TIMELINESS[3]

The potential of administering RV before rotavirus gastro-enteritis (RVGE) cases occur depends on providing each vaccine dose in time and in achieving high coverage with each dose before the peak of the disease incidence occurs.



Example – The figure on the left shows the shows the percentage of all RVGE hospital admissions aged less than 36 months that occurred in each week of age in a study in Blantyre, Malawi[4], when there was no rotavirus vaccination programme.

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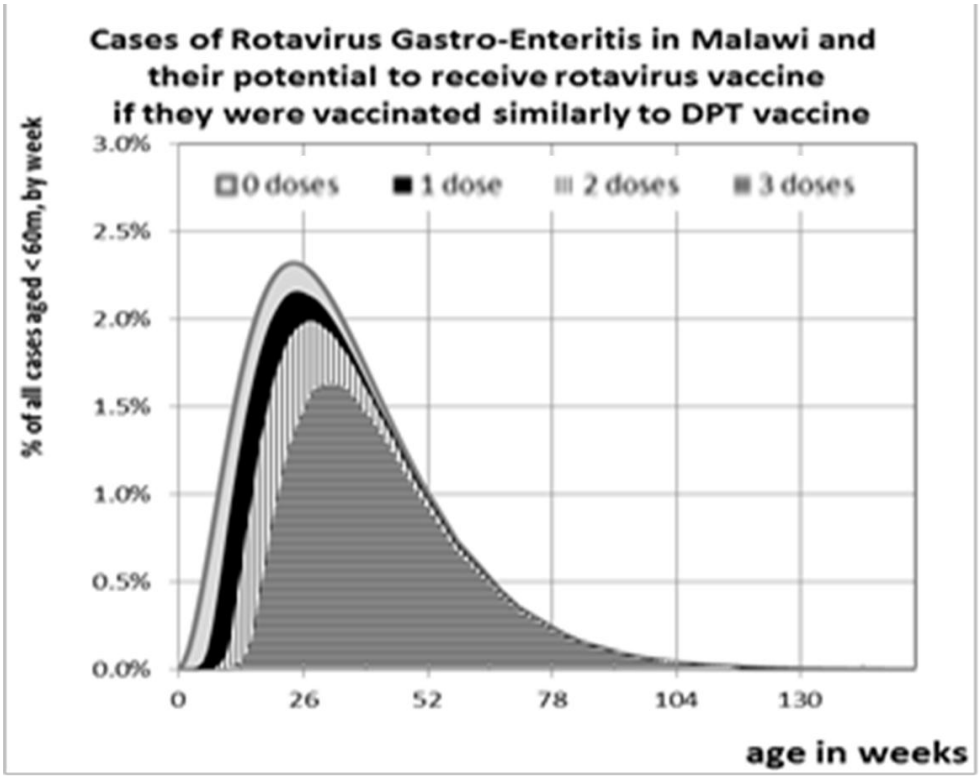
[2] Soares K et al (2012) Vaccines for preventing rotavirus diarrhoea: vaccines in use. COCHRANE review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008521.pub2/figures) and Soares K et al (2012) . Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines- Report to WHO/IVR.

[3] Sanderson C et al (2011) Global review of rotavirus morbidity and mortality data by age and WHO region. Report to WHO/IVR

[4] Cunliffe NA. Ngwira BM, Dove W, Thindwa BDM, Turner AM, Broadhead RL, Molyneux ME, Hart AC. Epidemiology of rotavirus infection in children in Blantyre, Malawi, 1997–2007. J Inf Dis 2010; 202(S1):S168–S174.



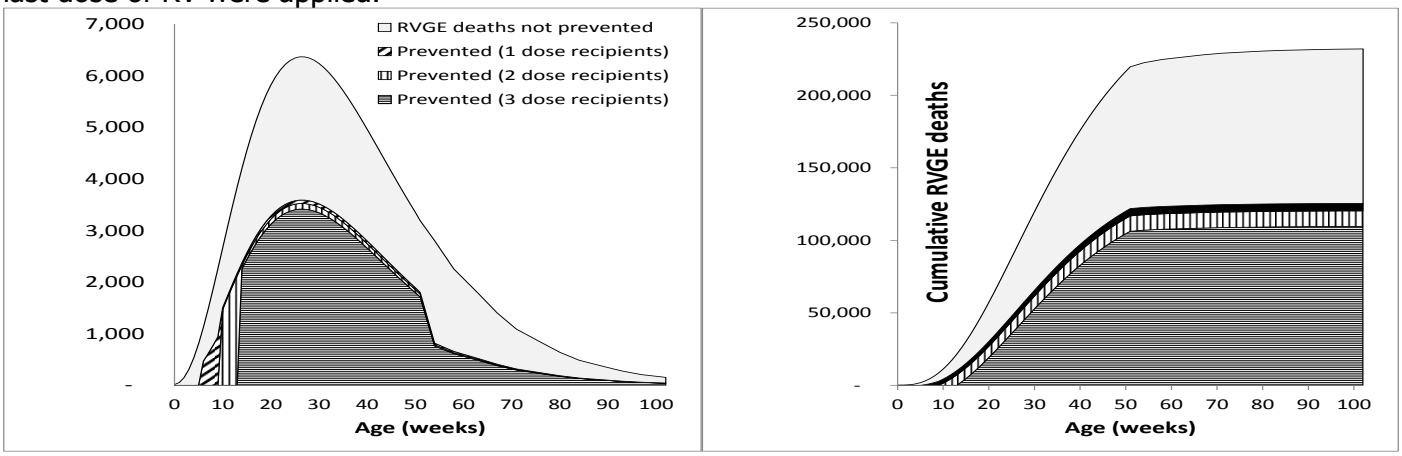
The figure on the left shows both the percentage of RVGE cases by week of age (outer line) and their potential to receive a given dose of RV given the frequency distribution of RV admissions with no vaccination programme.
The lighter outer area under the curve labeled `0 doses` shows the cases that would have had no vaccine doses at the time if the coverage had been the same as for DTP, ie ignoring the age restrictions.
The areas labeled '1 dose' and '2 doses' indicate the cases which would have had received 1 and 2 doses.

For a 3-dose vaccine, only the cases in the horizontal strikeout area would have received the number of doses intended by the programme. By 12 months of age 11.3% of the children would have not receive any dose or only 1 dose, only 25.0% of the potential RVGE cases would have received 2 doses and 43.5% would have received 3 doses. [To read more about this subject go to page 8]

POTENTIAL IMPACT OF ROTAVIRUS VACCINES[5]

As the potential of preventing RVGE deaths is a function of vaccine effectiveness, age specific distribution of deaths and coverage and timeliness, unless high coverage is achieved by the age when the peak of disease incidence occurs the impact will be much lower than anticipated

Example: The figure below on the left shows the number of RVGE deaths in children in Africa (stratum D and E) by week of age (outer line) and their potential to be protected with RV (doses received x vaccine effectiveness) if they were vaccinated similarly to DPT and if the current age restrictions for the first and last dose of RV were applied.



The figure on the right presents the same data as cumulative number of rotavirus deaths. The number of potential RVGE deaths prevented with 2 or 3 doses of RV vaccine would expand (i.e. expand the darker areas) if restrictions on age at administration are not enforced & if timeliness & coverage improves.
[To read more about this subject go to page 12]

[5] Sanderson C et al (2011) Global review of rotavirus morbidity and mortality data by age and WHO region. Report to WHO/IVR

ESTIMATED BENEFITS OF ROTAVIRUS VACCINES AND POTENTIAL RISKS AT GLOBAL LEVEL[6]

In low and middle-income WHO about 453,000 rotavirus-associated deaths are estimated among children younger than 5 annually without a rotavirus vaccination. The figure below on the left shows the estimated RVGE deaths avoided and the intussusception deaths occurring after RV administration with the current age restrictions recommendations and the estimated deaths avoided if current recommendations (age-restriction) were to be replaced with one where the vaccine can be given at any age (no age restriction).

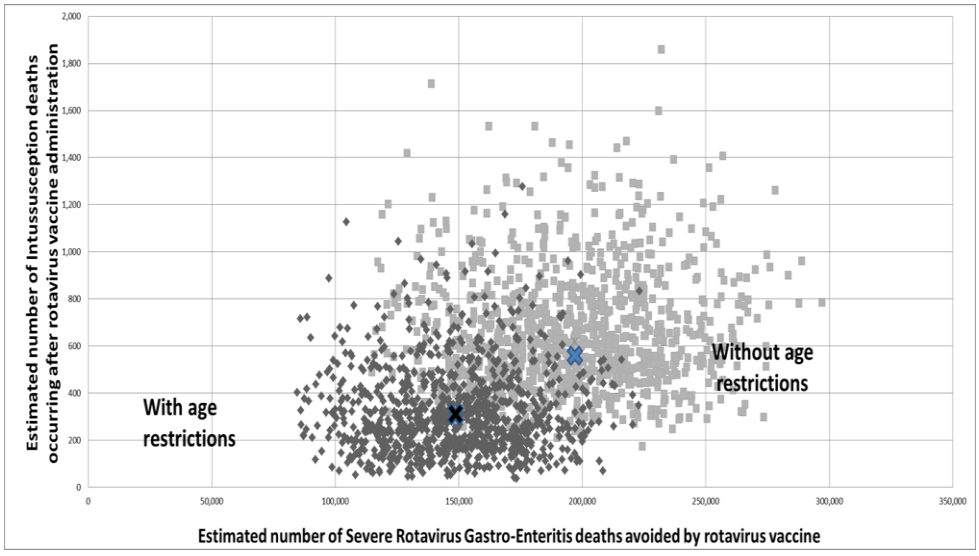
Table 2. Rotavirus deaths averted versus excess intussusception deaths caused under age-restricted and age-unrestricted rotavirus vaccination strategies, by WHO mortality stratum and age

	Rotavirus deaths averted (95% CI)			Intussusception deaths caused (95% CI)			Benefit to Risk Ratio
Vaccination strategy	Age restriction†	No age restriction	Excess	Age restriction†	No age restriction	Excess	
B & C countries							
Median	9,500	18,900	9,400	36	72	36	258
5th percentile	8,000	16,100	8,100	13	34	21	379
95th percentile	11,500	21,500	10,000	84	137	53	189
D: Americas							
Median	2,100	2,600	500	4	6	2	232
5th percentile	1,500	1,800	300	1	3	1	212
95th percentile	2,700	3,300	600	9	12	3	194
D: Asia							
Median	58,300	78,400	20,100	134	303	169	119
5th percentile	38,200	51,200	13,000	46	153	106	122
95th percentile	77,800	103,700	25,900	317	559	243	107
D: Africa							
Median	78,900	97,300	18,400	109	234	125	147
5th percentile	55,200	69,000	13,800	37	127	91	152
95th percentile	102,100	124,700	22,600	264	433	170	133
All stratum							
Median	148,600	196,900	48,400	285	618	333	145
5th percentile	103,600	138,700	35,100	98	318	220	160
95th percentile	193,800	252,900	59,100	678	1,148	470	126

* Estimates of rotavirus deaths averted and intussusception deaths caused are based on efficacy, risk, case-fatality parameters in Table 1. Vaccination coverage is based on diphtheria-tetanus-pertussis (DTP) vaccination rates from household Demographic Health Surveys and UNICEF Multiple Indicator Cluster Surveys.

† Age restriction denotes dose 1 administration by 15 weeks and the full series by 32 weeks of age

A model projects that a rotavirus vaccination program under the current age-restricted schedule would prevent almost 33% or 148,600 of the global deaths (5th–95th centiles, 103,600–193,800) if delivered at the same ages at which the DTP vaccine is currently being delivered in these countries. Without the age restrictions, a RV would prevent 48% or 196,900 deaths of all rotavirus deaths (138,700–252,900. A rotavirus vaccination program limiting vaccination to children < 14 weeks of age would result in about 285 intussusception deaths (98–678). Without age restrictions would cause 618 intussusception deaths (318–1,148). The median incremental benefit-risk ratio in all mortality strata was estimated at nearly 145 lives averted for every death caused, ranging from 119-258 lives averted for every death caused across the different mortality strata.



The figure on the right illustrates the relationship between the estimated number of Rotavirus Gastro-Enteritis deaths avoided by rotavirus vaccine and the estimated number of intussusception deaths occurring after RV administration. Estimates with age restrictions (black squares) and without age restrictions (gray squares) are shown. Given the uncertainty on key parameters the estimates spread out on the right side of the figure and clouds overlap.

Trade-offs exists when considering various policy options. On the benefits side, unrestricted schedule would prevent additional 48,400 rotavirus deaths due to ~23-25% increase in vaccine coverage. On the risks side, the unrestricted schedule is estimated to cause ~333 excess intussusception deaths compared to current age restricted schedule.

[To read more about this subject go to page 14]

[6] Patel M et al (2012). Age restrictions for rotavirus vaccination: evidence-based analysis of rotavirus mortality reduction versus risk of fatal intussusception by mortality stratum. Report to WHO/IVR; Patel M (2011) Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil New England Journal of Medicine 364:24 (2283-2292); Patel M et al (2009) broadening the age restrictions for initiating rotavirus vaccination in regions with high rotavirus mortality: benefits of mortality reduction versus risk of fatal intussusception Vaccine 27 (2916-2922).

EVIDENCE SUMMARIES

Summary of the evidence on rotavirus vaccines efficacy and effectiveness by WHO mortality strata [7]

OUTCOME OF INTEREST	Effect of rotavirus vaccine (RV) by WHO mortality strata				
	A	**B**	**C**	**D**	**E**
	Vaccine efficacy (%): RV1: -28 (-88 – 13) RV5: -24 (-132 - 31)	Vaccine efficacy (%): RV1: -32 (-91 - 9) RV5:-12 (-95 - 35)	Vaccine efficacy (%): No data available	Vaccine efficacy (%): RV1:-30 (-92 - 12) RV5: -3 (-27 - 26)	Vaccine efficacy (%) RV1:-24 (-5 - 46) RV5: -7 (-26 - 32)
All-cause mortality	**Weak evidence suggests that RV induces a non-significant reduction on all-cause mortality in any strata.** Data from 22 RCTs for RV1 and 6 RCTS for RV5 show no statistically significant reduction in any WHO mortality strata and no differences observed within strata. One observational study of RV1 reported a decline in children < 1 year and no difference in children 2-4 years. Caution: The RCTs were not powered to assess mortality and in 12 RCTs mortality was assessed for less than 2 months after vaccine given.				
Diarrhoeal mortality	No data available	Relative Risk Reduction (RRR): RV1: ~42% in children < 1 year old ~24%-54% in children 1-4 years old RV5: no data available	No data available	Incidence Rate Ratio (IRR): RV1: No data available RV5: 0.80 (0.61 – 1.04)	No data available
	Weak evidence, suggests RV likely result in a reduction in Diarrhoeal related mortality. Three observational studies (strata B) reported a reduction in the likelihood of Diarrhoeal deaths after rotavirus vaccine introduction. However, one observational study (strata D) reported non-statistically significant impact on Diarrhoeal mortality. Caution: Design limitations of observational studies need to be taken into account. These observational studies compared estimated Diarrhoeal related mortality 2-3 years after vaccine introduction with expected rates in 2-3 in the pre-vaccine era. No data on the actual age at vaccination is reported. Data is available only for Latin American countries.				
Severe Rotavirus Gastro-Enteritis	Vaccine efficacy (%): RV1 – 1st year: 89 (82– 93) 2nd year: 90 (86-93) RV5 – 1st year: 93 (49-99) 2nd year: 91 (66-97)	Vaccine efficacy (%): RV1 – 1st year: 79 (71-86) 2nd year: 78 (-29-96) RV5 – 1st year: 51 (15-71) 2nd year: 52 (31-67)	No data available	Vaccine efficacy (%): RV1 – 1st year: 85 (72-92) 2nd year: no data RV5 – 1st year: 58 (40-71) 2nd year: 44 (30-55)	Vaccine efficacy (%): RV1 – 1st year: 61 (45-72) 2nd year: 59 (90-81) RV5 – 1st year: 64 (41– 78) 2nd year: 39 (20-54)
	Moderate evidence suggests that both rotavirus vaccines are efficacious however, data shows that they are more efficacious in low mortality under five mortality settings Data from 11 RCTs of RV1 and 6 RCTs of RV5 with one and/or two years follow up (in all strata except C strata). RV1 was highly efficacious in all strata but clear gradient is observed with vaccine efficacy declining among strata. RV5 is highly efficacious in strata A and, only moderately efficacious in strata B, D and E. Caution: Four large RCTs contributed data to one more than one strata. Three RCTs only followed up a subset of the initial sample during the second year. These data excludes observational studies on SRVGE that did not report data on various schedules used.				
Rotavirus diarrhoea health care encounters	Vaccine efficacy (%) RV1: RV5 : 96	No data available	No data available	No data available	No data available
	Weak evidence suggests that both rotavirus vaccines possible result in a reduction of related health care encounters. Two observational studies (Stratum A) reported data on different schedules and their impact on rotavirus diarrhoea health care encounters after RV1 and/or RV5. Another observational study reported a reduction in number of RV positive children but no formal statistical analysis was reported. Caution: Design limitations of observational studies need to be taken into account.				

[7] Soares K et al (2012) Vaccines for preventing rotavirus diarrhoea: vaccines in use. COCHRANE review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008521.pub2/figures) and Soares K et al (2012). Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines- Report to WHO/IVR

Key findings on effect of the number of doses of rotavirus vaccines on selected disease outcomes[8]

Outcome	Effect of rotavirus vaccine (RV) by WHO mortality strata				
	A	B	C	D	E
All-cause mortality	No data available	No data available	No data available	No data available	Relative Risk: RV1: 0.5 (0.05-5.50) RV5: no data
Diarrhoeal mortality	No data available	No data available	No data available	No data available	No data available
Severe rotavirus gastro-enteritis	No data available	No data available	No data available	No data available	Vaccine efficacy (%) RV1- 1st year: 6 (-56-43) 2nd year: 78 (-1-95)
Rotavirus diarrhoea health care encounters	Odds Ratio RV1 1 vs 0 dose: 0.61 (0.36-1.06) 2 vs 0 dose: 0.40 (0.20-0.81) RV5 1 vs 0 dose: 0.34 (0.2-0.59) 2 vs 0 dose: 0.24 (0.14-0.40) 3 vs 0 dose: 0.18 (0.11-0.29)	Odds Ratio RV1 1 vs 0 dose: 0.61 (0.36-1.06) 2 vs 0 dose: 0.40 (0.20-0.81) RV5 - no data	No data available	Odds Ratio RV1-no data RV5 1 vs 0 dose: 0.34 (0.2-0.59) 2 vs 0 dose: 0.24 (0.14-0.40) 3 vs 0 dose: 0.18 (0.11-0.29)	No data available
Overall findings	**Weak evidence to conclude that giving a 3rd dose or RV1 is superior to the currently recommended 2 dose schedule.** **Very weak evidence from observational studies suggests that children receiving fewer than the recommended number of doses also have a level of protection against rotavirus Diarrhoeal health care encounters.** One RCT (stratum E) of RV1 comparing 3 doses versus 2 doses reported non-statistically significant difference after 6 months follow up. No data from RV5 on impact of number of doses in all-cause mortality. Two RCTs (stratum E) on SRVGE comparing 3 to 2 doses of RV1 versus placebo showed non statistical significant difference at one year follow up. In the 2nd year follow up of a subset in one RCT showed a non-significant higher vaccine efficacy when a 3rd dose was added. Twenty-two observational studies reported data on rotavirus Diarrhoeal health care encounters, three of them in stratum A and one in stratum B. Four observational studies (stratum A, B & D) reported data on effect of RV1 on rotavirus diarrhoea health care encounters reported a trend for the effect size to increase with increasing number of doses. Caution: RCT data is only available for stratum E. Design limitations of observational studies apply.				

[8] Soares K et al (2012) Vaccines for preventing rotavirus diarrhoea: vaccines in use. COCHRANE review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008521.pub2/figures) and Soares K et al (2012). Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines- Report to WHO/IVR

Key findings on effect of the age at the first dose of rotavirus vaccines on selected disease outcomes[9]

Outcome	Effect of rotavirus vaccine (RV) by WHO mortality strata				
	A	B	C	D	E
All-cause mortality	No data available	Relative risk (RR) RV1- 2.82 (0.56-14.4)	No data available	No data available	Relative risk (RR) RV1- 2.82 (0.56-14.4)
Diarrhoeal mortality	No data available	No data available	No data available	No data available	No data available
Severe rotavirus gastro-enteritis	No data on direct comparisons available	No data on direct comparisons available	No data on direct comparisons available	No data on direct comparisons available	Relative Risk (RR) RV1- 1st year: 1.28 (0.34-4.71) 2nd year: 0.22 (0.05-1.01)
Rotavirus diarrhoea health care encounters	No data available	No data available	No data available	No data available	No data available
Overall findings	**Weak evidence based on direct comparisons to assess the effect of age at administration on any of the outcomes evaluated.** Three RCTs (stratum B and E) compared different ages at 1st vaccine dose for RV1 (6-7 weeks versus 10-11 weeks of age) reported non-statistically significant differences in all-cause mortality. Indirect comparisons of three small RCTs of RV1 and RV5 showed no impact for mortality for different ages at first dose. No data from observational studies are available. Two RCTs (stratum E) of RV1 assessing effect of age at 1st dose on SRGE reported non-statistically significant differences for children receiving the first dose 6 versus 10-11 weeks of age during the 1st year follow up. During the second year follow up (only the Malawi cohort) showed non-statistically significant differences. Indirect comparisons (stratum A, B, D, E) based on stratification of RV1 and RV5 RCTs using different schedules showed efficacy against SRGE for various ages at 1st dose except for children receiving the 1st dose of RV1 at 10 weeks of age or RV5 at ages 8, 9, 10 weeks. Caution: RCTs not powered to observe an effect on mortality. Except from the 2 small RCTs assessing SRVGE mentioned above there is no additional data. RCTs not designed to measure a difference among schedules.				

[9] Soares K et al (2012) Vaccines for preventing rotavirus diarrhoea: vaccines in use. COCHRANE review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008521.pub2/figures) and Soares K et al (2012). Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines- Report to WHO/IVR

Key findings on effect co-administration of rotavirus vaccines with other vaccines on selected disease outcomes[10]

Outcome	Effect of rotavirus vaccine (RV) by WHO mortality strata				
	A	B	C	D	E
All-cause mortality	No data available	Relative Risk (RR) OPV+RV5 versus RV5: 0.98 (0.06-15.54)	No data available	Relative Risk (RR) OPV+RV1 versus RV1:0.33 (0.01-7.92) OPV+RV5 versus RV5: 0.98 (0.06-15.54)	Relative Risk (RR) OPV+RV1 versus IPV + RV1:0.50 (0.05-5.46)
Diarrheal mortality	No data available	No data available	No data available	No data available	No data available
Severe rotavirus gastro-enteritis	No data available	No data available	No data available	No data available	No data available
Rotavirus diarrhoea health care encounters	No data available	No data available	No data available	No data available	No data available
Overall findings	**Weak evidence suggest that there is no statistically significant differences on effect on outcomes assessed when RV is administered alone or concomitantly with other vaccines** Two RCTs (stratum D and E) comparing concomitant use of OPV with RV1 versus RV1 alone or, OPV with RV1 versus IPV with RV1 showed no impact in all-cause mortality. One small RCT (Stratum B and D) comparing RV5 plus OPV with RV5 alone also showed no impact on all-cause mortality. Indirect comparisons based on stratification of RCTs of Rv1 and Rv5 showed not significant impact on all-cause mortality for RCTs in which all vaccines were allowed or in RCTs that did not allowed concomitant use of OPV or IPV or, RCTs that did not allowed concomitant use of any other childhood vaccines. No data from observational studies are available. No data on effect on SRVGE from RCTs or observational studies of RV1 and RV5 are available that directly compared simultaneous vaccination with other childhood vaccines. Indirect comparisons from stratification of RV1 and RV5 RCTs grouped as to whether concomitant administration of RV was allowed with any other vaccine and its effect on SVRGE was not observed. Caution: Small sample size of RCT may explain the findings.				

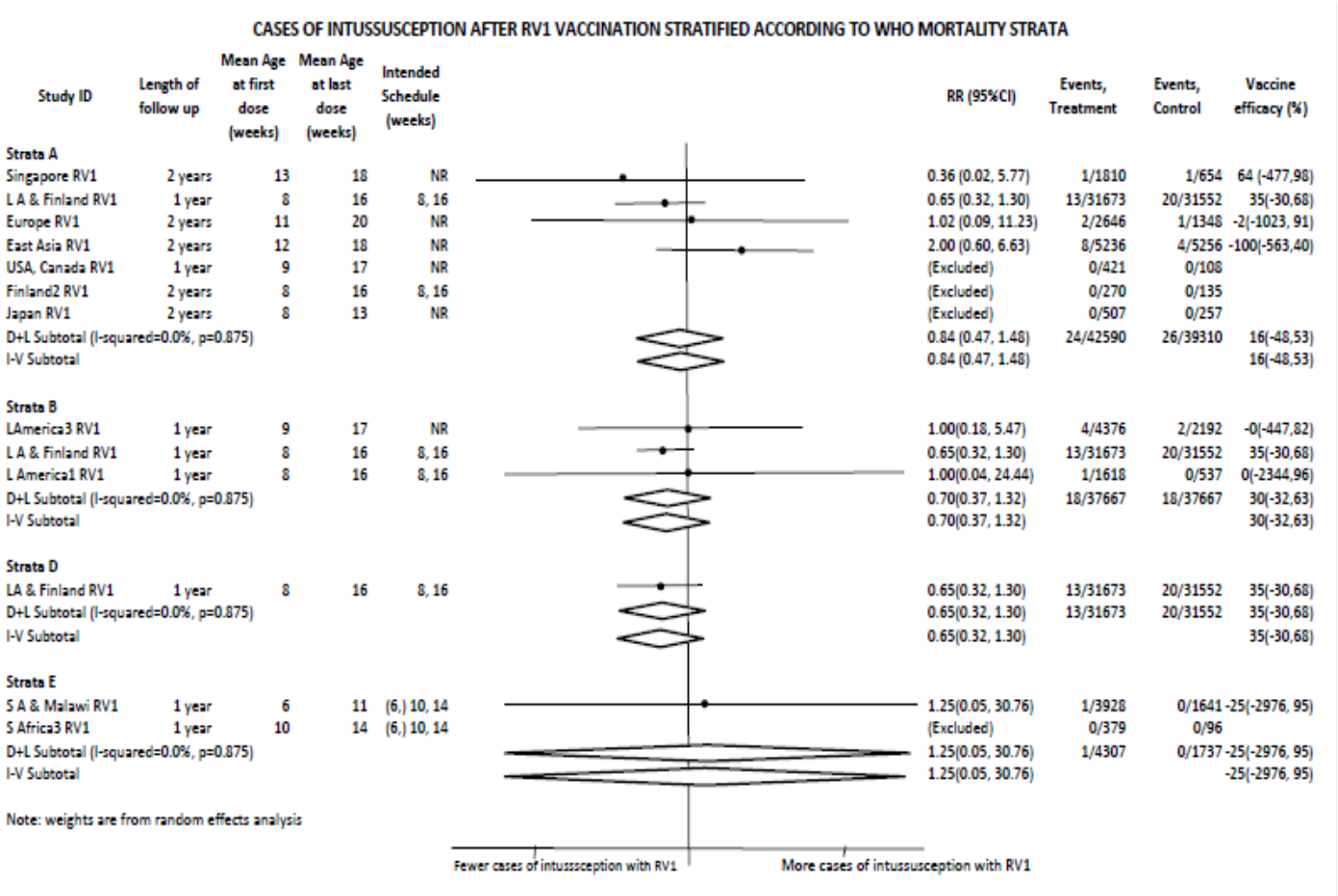
[10] Soares K et al (2012) Vaccines for preventing rotavirus diarrhoea: vaccines in use. COCHRANE review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008521.pub2/figures) and Soares K et al (2012). Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines- Report to WHO/IVR

Key findings on rotavirus vaccines safety by WHO mortality strata[11]

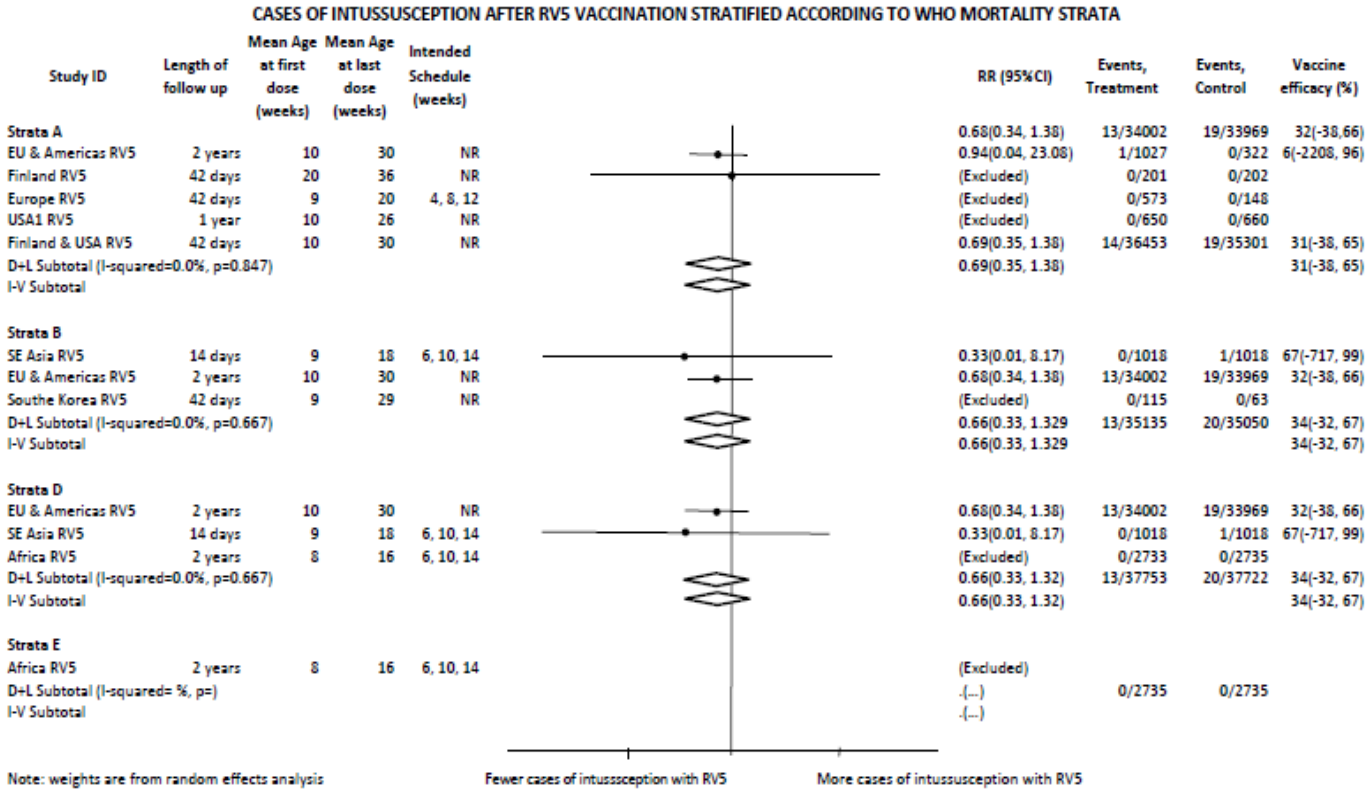
The current evidence is weak, based on direct comparison of RV1 and RV5 RCTs that were not powered to identify rare events such as cases of intussusception, and a few surveillance studies performed mainly in countries on strata A and B.

There is 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. 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 a study in Australia.

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 show 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. None of the RCTs were powered to identify such a rare adverse event like intussusception.



[11] Soares K et al (2012) Vaccines for preventing rotavirus diarrhoea: vaccines in use. COCHRANE review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008521.pub2/figures) and Soares K et al (2012). Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines- Report to WHO/IVR



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. 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. 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 reported information only in an abstract and reported no statistically significant association between RV1 and intussusception in Mexico and Singapore. In addition, a recently published surveillance study from Mexico (Mexico3 RV1 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. 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 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 the table below.

RISK OF INTUSSUSCEPTION AFTER ROTAVIRUS VACCINES ADMINISTRATION– DATA AFTER EACH VACCINE DOSE, FROM 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
						# cases	#controls			
Dose 1										
Australia3 RV1-RV5[12] (RV1 data)	A	Surveillance	2, 4 months	According to Brighton Collaboration definition from questionnaires to doctors or reported by study nurses.	1-7 days	3/154289 doses	0.87 expected[13]	RR	3.45 (0.71, 1.01)	Children's age 1-3 months
Australia3 RV1-RV5 (RV1 data)	A	Surveillance	2, 4 months		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)[14]	13 expected[15]	Rate Ratio[16]	0.83 (0.34, 2.01)	Children's age 6-14 wks

[12] 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.

[13] 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.

[14] 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.

[15] 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.

[16] 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		1-7 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
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[17]	SIR[18]	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
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

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

[18] 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
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
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	52 expected	Rate Ratio	0.35 (0.18-	Children's age 15-23

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
						reported)			0.67)	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
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

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	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)	

Overview of Rotavirus disease epidemiology and potential to provide one or more doses of vaccine by week of age

Burden of Disease[19]

As of January 2012, the World Health Organization estimates that globally 453 000 (420 000 - 494 000) child deaths occurred during 2008 due to rotavirus infection. National estimates of rotavirus attributable deaths among children under five years of age ranged from 98 621 (India) to fewer than 5 deaths (74 countries). Twenty-two per cent of all rotavirus deaths under five years of age occurred in India. Five countries (India, Nigeria, the Democratic Republic of the Congo, Ethiopia and Pakistan) accounted for more than half of all rota deaths under age five in 2008. Globally these 453 000 child rotavirus deaths accounted for approximately 5% of all child deaths and the cause-specific mortality rate (rotavirus deaths under age five per 100 000 population under age five) was 86. National cause-specific mortality rates ranged from 474 (Afghanistan) to less than 1 (63 countries). Four countries - Afghanistan, Burundi, Chad and Somalia had a less than five rotavirus mortality rate of greater than 300.

Age-specific distribution of key outcomes in children [20]

Global review of rotavirus morbidity and mortality data by age and WHO region

Aim: To assemble existing data on age at RVGE and examine it using age groups small enough for assessment of the population impact of rotavirus vaccination according to different schedules.
Methods: Identify researchers in the field through literature review and informal methods. Contact them and seek their cooperation in supplying RVGE age distributions or suitable raw data. Assemble the data. Fit gamma distributions to summarise the data from each study and deal with reporting anomalies. Conduct meta-analyses to summarise the data from all the populations, and meta-regressions to identify factors related to age at RVGE. Compare age distributions for RVGE admissions with those for RVGE deaths, RVGE cases in the community, and 'any diarrhoea'. For countries with survey data on age-specific vaccine coverage, construct age/protection profiles to aid assessment of the timeliness of vaccination in relation to age at RVGE.
Results: The pooled estimates of the percentages of all RVGE events in children less than 3 years old which had occurred by age 6, 9, 13, 15 and 17, 26 and 32 weeks respectively were 1%, 3%, 6%, 8%, 10%, 22% and 32%. However there was substantial heterogeneity, with 3 studies that could be considered as outliers. Infant mortality was linked only to RVGE events before age 32 weeks. The evidence for relationship between exclusive breast feeding for 6 months and RVGE events before 6 weeks of age was in the expected direction, but very weak indeed. There were only two distributions of ages at death from RVGE and they were based on very small numbers, but they were not dissimilar to those for age at RV admission in the same populations. Two sources provided distributions for ambulatory and hospitalised cases in the same populations; in one case the distributions were almost identical, and in the other they were reasonably similar. The age distributions for admission with RVGE and any diarrhoea were very similar in the 5 SEARO surveillance studies, but the correspondence was less clear in the two studies from other regions.
Conclusion: In many parts of the world there are relatively few admissions for RVGE before the scheduled first dose of vaccine. However in some populations RVGE in very young children is more common and EPI coverage is low or delayed. In these circumstances the benefits of a rotavirus vaccine programme will be materially reduced. Also it seems that children in the poorest, typically rural, households with the highest risk of mortality may have the earliest exposure to rotavirus and the lowest level of vaccine protection. Ideally vaccination schedules should be designed to provide benefits to those at highest risk. This might imply extending the evidence base to age distributions for different socio-economic groups.

[19] http://www.who.int/immunization_monitoring/burden/rotavirus_estimates/en/index.html
[20] Sanderson C et al (2011) Global review of rotavirus morbidity and mortality data by age and WHO region. Report to WHO/IVR

Overview of the estimated impact of rotavirus vaccines on Severe Rotavirus Gastro-Enteritis and estimated risk of fatal intussusception after rotavirus vaccination[21]

Aim: To assess and compare the potential benefits for mortality reduction from rotavirus versus the risk of fatal intussusception for an age restricted and unrestricted vaccination policy in WHO countries with low and high child mortality.

Methods: This analysis modeled the number of rotavirus deaths prevented by rotavirus vaccination and the number of intussusception deaths caused by vaccination when administered on the current restricted schedule versus an unrestricted schedule whereby rotavirus vaccine would be administered with DTP vaccine up to age 3 years. Countries were grouped by WHO child mortality strata. Inputs were stratum-specific estimates of rotavirus mortality, intussusception mortality, and predicted vaccination rates by week of age, and vaccine efficacy and vaccine-associated intussusception risk.

Findings: The model estimated that a restricted schedule would prevent 148,600 rotavirus deaths (5th-–95th centiles, 103,600–193,800) while causing 285 intussusception deaths (98–678). Vaccination without age restrictions would prevent 196,900 rotavirus deaths (138,700–252,900) while causing 618 intussusception deaths (318–1,148). Without the age restrictions vaccination would avert an additional 184 rotavirus deaths for every intussusception death caused by vaccine, for a net benefit of 48,100 additional lives (34,900–58,600) prevented by vaccination. These additional deaths prevented under an unrestricted versus restricted schedule reflect additional 21%-28% children who would potentially be eligible for rotavirus vaccine. The number of additional rotavirus deaths averted and intussusception deaths caused by vaccination varied by WHO mortality are as follows:

- ➔ B& C countries: 9,400 (8,100-10,000 versus 36 (21-53)
- ➔ D-Americas: 500 (300-600) versus 2 (1-3)
- ➔ D-Asia: 20,100 (13,000-25,900) versus 169 (106-243)
- ➔ D&E-Africa: 18,400 (13,800-22,600) versus 125 (91-170)

Interpretation: In low and middle-income countries, the additional lives saved by removing age restrictions for rotavirus vaccination would outnumber the excess vaccine-associated intussusception deaths.

Limitations of the analyses: The benefit-risk estimates could be conservative and err on the side of risk for three reasons: over 45 publications have documented remarkable declines in severe diarrhea and rotavirus disease, including deaths, since their introduction in national immunization programs worldwide. Many of these studies from different locations have demonstrated significant declines in unvaccinated members of the community, indicating indirect benefits of vaccination which were not accounted for in the mode. It was assumed that some risk of intussusception exists in all countries worldwide, including with dose 2; however, risk of intussusception has varied by setting and robust studies in 2 large countries have not identified risk after dose 1. Eve in the base scenario, high rates of intussusception case-fatality were assumed in all WHO regions, about two-fold higher than those reported in the literature. The benefit risk ratios might be inflated due to several factors: The base scenario assumed that the relative risk of intussusception relative to background does not increase with age. While limited data from an evaluation in Mexico does not suggest effect modification of risk for current vaccines by age, we incorporated a scenario of increased risk with age at vaccination which indicated that vaccination would avert 66 rotavirus deaths for each excess intussusception death.

[21] Patel M et al (2012). Age restrictions for rotavirus vaccination: evidence-based analysis of rotavirus mortality reduction versus risk of fatal intussusception by mortality stratum. Report to WHO/IVR

GRADE Assessment of the quality of evidence

Is there evidence a) that giving a third dose of RV1 is superior to the currently recommended 2-dose schedule, and b) that partial vaccination is also efficacious against severe rotavirus diarrhoea?					
			Rating	Adjustment to score	
				a) 3p x 2p	b) Partial schedule
Quality Assessment	No of studies/starting score		● 2 RCTs directly comparing 3p x 2p (RV1) ● 1 RCT (RV5), 16 observational (4 RV1, 10 RV5 and 2 RV1-RV5) indirect comparisons[22]	4	2
	Factors decreasing confidence	Limitation in study design	Serious[23]	3	1
		Inconsistency	Serious[24]	2	1
		Indirectness	Serious[25] (not relevant for 3p x 2p)	2	1
		Imprecision	Serious[26]	1	1
		Publication bias	Serious[27]	1	1
	Factors increasing confidence	Strength of association	No large effect	1	1
		Dose-response	No	1	1
		Mitigated bias and confounding	No	1	1
	Final numerical score of quality of evidence			1	1
Summary of findings	**Statement on quality of evidence**		**We have very little confidence in the estimates of the effect on severe rotavirus diarrhoea and rotavirus diarrhoea related health care encounters after different doses of rotavirus vaccine.**		
	Conclusion		**There is no conclusive evidence that giving a third dose of RV1 is superior to the currently recommended 2-dose schedule.** **Very weak evidence from observational studies suggests that children receiving fewer than the recommended number of doses also have a level of protection against rotavirus diarrhoea related health care encounters.**		

[22] The RCTs *South Africa3 RV1* and *South Africa and Malawi RV1* directly compared 2 and 3 doses of RV1. The RCT post-hoc analysis *Europe and the Americas RV5* reported efficacy for children receiving one or two doses of RV5 starts at 2 points together with the observational studies.

[23] Allocation concealment was not reported for 2 of the 3 included RCTs. In addition, 3 of the 12 included observational studies that could be pooled did not take both of the confounders *age* and *community* into account.

[24] 45% heterogeneity (I^2) was found for the direct comparison at one year follow-up and above 45% for 3 of the 5 indirect comparisons for observational studies.

[25] Only *South Africa3 RV1* and *South Africa and Malawi RV1* directly compared different doses. The RCT post-hoc analysis *Europe and the Americas RV5* and the observational studies did not directly compare different doses, only a certain dose against placebo, and can therefore only provide indirect comparisons.

[26] The direct comparison between 3 and 2 doses and the post-hoc RCT analysis of efficacy after each dose have very wide 95% confidence intervals. Only one of the RCTs with a direct comparison, *South Africa and Malawi RV1*, was designed to measure efficacy.

[27] Publication bias is likely as only two studies were found that directly compared vaccine efficacy after different number of rotavirus vaccine doses.

Is there evidence a) that lifting the currently recommended age window for rotavirus vaccine administration is safe, and b) that administering the first dose of vaccine at different ages is safe?					
			Rating	Adjustment to score	
				a) no age restric-tion	b) differen t ages
Quality Assessment	No of studies/starting score		● No RCTs or observational studies reported on safety outside the currently recommended age windows ● 1 RCT direct comparison (RV1), ● 37 RCTs indirect comparisons (27 RV1, 10 RV5)[28]	-	4
	Factors decreasing confidence	Limitation in study design	Serious[29]	-	3
		Inconsistency	None serious	-	3
		Indirectness	Serious[30]	-	2
		Imprecision	Serious[31]	-	1
		Publication bias	Serious[32]	-	1
	Factors increasing confidence	Strength of association	No large effect	-	1
		Dose-response	No	-	1
		Mitigated bias and confounding	No	-	1
	Final numerical score of quality of evidence			-	1
Summary of findings	**Statement on quality of evidence**		**We have very little confidence in the estimates of the effect on safety for different age at first vaccine dose.**		
	Conclusion		**There is no evidence that lifting the currently recommended age window for rotavirus vaccine administration is unsafe. Weak evidence comparing RCTs administering the first and last dose in different ages (all inside the recommended age window) have not shown any impact of age on serious adverse events or intussusception. Weak evidence from RCTs has not shown an increase risk of intussusception 1-7 or 1-42 days after vaccination. Weak evidence from observational studies showed an excess of intussusception cases after rotavirus vaccine doses were given in Brazil, Mexico and Australia.**		

[28] Only one RCT reporting safety outcomes, *South Africa3 RV1*, directly compared different ages at first rotavirus vaccine dose. No observational studies reporting safety outcomes compared different age at vaccine administration.
[29] Risk of bias, mainly no report of allocation concealment but also risk of blinding and attrition bias, was found for 27 of the 37 included RCTs.
[30] Only *South Africa3 RV1* directly compared serious adverse events for different ages (6 or 10 weeks) at first vaccine dose. The remaining RCTs were stratified according to age at first vaccine dose and can therefore only provide indirect comparisons.
[31] The direct comparison of different age at first vaccine dose have wide 95% confidence intervals, as do 3 of the 11 indirect comparisons.
[32] Publication bias is likely as only one study was found that directly compared vaccine safety for different ages at first vaccine dose.

ROTAVIRUS VACCINES: WHO Recommendations for Routine Immunization (2009)

(http://www.who.int/immunization/documents/positionpapers/en/)

"(…) Given the background rate of natural intussusception and the large number of children involved in national immunization programmes, intussusception cases by chance alone are expected to occur following rotavirus vaccination. However, as natural intussusception usually spares infants aged <12 weeks, the first dose of the current rotavirus vaccines is recommended to be administered before that age. The apparent absence of an increased risk of intussusception associated with the current rotavirus vaccines might reflect the age at which they are administered. The current rotavirus vaccines should not be used in catch-up vaccination campaigns, where the exact age of the vaccinees may be difficult to ascertain and there is the danger that a first dose may mistakenly be given to children >12 weeks of age. (…). In low-income developing countries, rotavirus vaccines can also be a cost-effective intervention. However, decision-making about the introduction of rotavirus vaccines in developing countries should consider, beyond cost-effectiveness, issues of affordability of the vaccine, considerations about its financial and operational impact on the immunization delivery system, and careful examination of current immunization practices, particularly with regard to age at vaccination. Rotavirus vaccines present the characteristic of not being indicated beyond 12 weeks of age for the first dose and beyond 24 (Rotarix™) or 32 (RotaTeq™) weeks of age for completing the series. It is important that immunization programme managers be aware of this constraint and that those who administer such vaccines are trained to observe the upper age limits placed on the first and last doses of the vaccination series. Children who did not complete the 2-dose schedule due to age should have this recorded on their immunization cards. In April 2007, SAGE reviewed the timing of vaccination in the developing world and found that in many countries a substantial proportion of infants receive their first dose of vaccine after 12 weeks of age. Rotavirus vaccination, if scheduled to be given at the same time as DTP/OPV vaccination, will reach a higher coverage in countries that immunize a large proportion of their infants before 12 weeks of age. The current rotavirus immunization schedule represents an opportunity to improve the timeliness of routine vaccination.

Recommended Routine Immunizations for Children

(http://www.who.int/immunization/policy/Immunization_routine_table2.pdf)

Antigen		Age at 1st dose	Doses in primary series	Interval between doses		Considerations (see below)
				1st to 2nd	2nd to 3rd	
Rotavirus[7]	Rotarix RV1	6 weeks (min with DTP1 15 weeks (max)	2	4 weeks (min) with DTP2 No later than 32 weeks of age		Maximum age limits for starting/completing vaccination.
	Rota Teq RV5	6 weeks (min with DTP1 15 weeks (max)	3	4 weeks (min) – 10 weeks with DTP2	4 weeks (min) with DTP3 no later than 32 weeks of age	

Considerations:

- Recommended to be included in all national immunization programmes. Rotarix vaccine is administered orally in a 2-dose schedule with the first and second doses of DTP. RotaTeq requires an oral 3-dose schedule with DTP1, DTP2, and DTP3 with an interval of 4-10 weeks between doses.
- First dose for either Rota Teq or Rotarix be administered at age 6-15 weeks. The maximum age for administering the last dose of either vaccine should be 32 weeks. The use of rotavirus vaccines should be part of a comprehensive strategy to control diarrhoeal diseases and should include, among other interventions, improvements in hygiene and sanitation, zinc supplementation, community-based administration of oral rehydration solution and overall improvements in case management.

WHO Prequalified rotavirus vaccines and approved schedules

(http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html)

Vaccine name	G1	G2	G3	G4	G9	P4	P8	Infants
RV1 **Rotarix™** (oral suspension, liquid or lyophilized + diluent) (for children from age 6 weeks)	X	X	X	X	X	X	X	• 2 doses, 1st dose as early as 6 weeks of age. • Minimum 4 weeks between doses • Preferably given before 16 weeks of age • Must be completed by the age of 24 weeks
RV5 **Rotateq ™** **xxxxxxxx**	X	X	X	X			X	• 3 doses, 1st dose at 6 to 12 weeks of age • Intervals between doses of 4 to 10 weeks • Third dose completed by 32 weeks of age