Grade Table 5: Is giving a third dose of RV1 superior to the currently recommended 2-dose schedule? [i]

PICO question: Is giving a third dose of RV1 superior to the currently recommended 2-dose schedule?				
			Rating	Adjustment to score
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[ii]	4
	Factors decreasing confidence	Limitation in study design	Serious[iii]	-1
		Inconsistency	Serious[iv]	-1
		Indirectness	Serious[v] (not relevant for 3p x 2p)	-1
		Imprecision	Serious[vi]	-1
		Publication bias	Serious[vii]	-1
	Factors increasing confidence	Strength of association	No large effect	0
		Dose-response	No	0
		Mitigated bias and confounding	No	0
	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 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.**	

[i] Adapted from Soares-Weiser K et al: 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 2012.

[ii] 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.

[iii] 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.

[iv] 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.

[v] 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.

[vi] 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.

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

Grade Table 6: Is partial vaccination also efficacious against severe rotavirus diarrhoea?[i]

PICO question: Is partial vaccination also efficacious against severe rotavirus diarrhoea?				
			Rating	Adjustment to score
Quality Assessment	No of studies/starting score		• 1RCT, 16 observational studies (4 RV1, 10 RV5 and 2 RV1-RV5)	2
	Factors decreasing confidence	Limitation in study design	Serious[ii]	-1
		Inconsistency	Serious[iii]	-1
		Indirectness	Serious[iv] (not relevant for 3p x 2p)	-1
		Imprecision	Serious[v]	-1
		Publication bias	Serious[vi]	-1
	Factors increasing confidence	Strength of association	No large effect	0
		Dose-response	No	0
		Mitigated bias and confounding	No	0
	Final numerical score of quality of evidence			1
Summary of findings	**Statement on quality of evidence**		**Very low: We have very little confidence in the estimates of the effect of partial vaccination on severe rotavirus diarrhoea and rotavirus diarrhoea-related health care encounters.**	
	Conclusion		**Very weak evidence from observational studies suggests that children receiving fewer than the recommended number of doses have some protection against rotavirus-diarrhoea-related health care encounters.**	

[i] Adapted from Soares-Weiser K et al: 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 2012.

[ii] 3 of the 12 included observational studies that could be pooled did not take both of the confounders *age* and *community* into account.

[iii] 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.

[iv] 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.

[v] 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.

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