Grading of scientific evidence – Tables 1–4: Does RV1and RV5 induce protection against rotavirus morbidity and mortality in young children both in low and highmortality settings?

Table 1: EFFECTIVENESS OF RV1 FOR PREVENTING ROTAVIRUS DIARRHOEA IN LOW-MORTALITY COUNTRIES CONSIDERING THE FOLLOWING OUTCOMES: A): SEVERE ROTAVIRUS DIARRHOEA; B) SEVERE EPISODES OF ALL-CAUSE DIARRHOEA; C) ALL-CAUSE DEATH [1]

Outcome A: Severe rotavirus diarrhoea episodes (follow up: up to 2 years)

WHAT IS THE EFFECT OF RV1 COMPARED TO PLACEBO FOR PREVENTING ROTAVIRUS DIARRHOEA IN LOW-MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		8 studies-all RCTs (32,854 participants)[2]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	none	0
		Imprecision	none	0
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR: 0.15 (0.12-0.2)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			Further research is unlikely to change our confidence in the estimate of effect
	Conclusion			We are confident that use of RV1 in low mortality countries reduces the rate of severe rotavirus diarrhoea

[1] Adapted from Soares-Weiser K, MacLehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD008521. DOI: 10.1002/14651858.CD008521.pub3.

[2] RV1 Bernstein 1999-USA; GSK (024)2008 LA; RV1 Kawamura 2010-JPN; RV1 Phua 2009-AS; RV1 Ruiz-Palac 06-LA/EU; RV1 Salinas 2005 LA; RV1 Vesikari-2004b-FIN; RV1 Vesikari-2007a-EU

Table 1, Outcome B: Severe episodes of all-cause diarrhoea (follow up: up to 2 years)

PICO Question: WHAT IS THE EFFECT OF RV1 COMPARED TO PLACEBO FOR PREVENTING ALL-CAUSE DIARRHOEA IN LOW-MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCTs (39,091 participants)[3]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	none	0
		Imprecision	none	0
		Publication bias	serious[4]	-1
	Factors increasing confidence	Strength of association/ large effect	RR: 0.60 (0.5-0.72)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			Further research may change the estimate of effect
	Conclusion			We are moderately confident that use of RV1 in low mortality countries reduces episodes of all- cause diarrhoea.

[3] RV1 Phua 2009-AS; RV1 Ruiz-Palac 06-LA/EU

[4] Risk of publication bias because the majority of studies did not provide data for this outcome

Table 1, Outcome C: All-cause death (Follow-up 2 months to 2 years)

PICO Question: WHAT IS THE EFFECT OF RV1 COMPARED TO PLACEBO FOR PREVENTING ALL-CAUSE DEATH IN LOW-MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		18 RCTs (93,321 participants)[5]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	none	0
		Imprecision	very serious[6]	-2
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR: 1.27 (0.89-1.81)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Further research is likely to change the estimate of effect.
	Conclusion			We are not certain about the effect of use of RV1 on all-cause death in low mortality countries

[5] RV1 Anh 2011-PHL; RV1 Anh 2011-VNM; RV1 Bernstein 1999-USA; RV1 GSK (021) 2007-PAN; RV1 GSK (024) 2008-LA; RV1 GSK (041) 2007-KOR; RV1 GSK (101555) 2008-PHIL; RV1 Kawamura 2010-JPN; RV1 Kerdpanich 2010-THA; RV1 Phua 2005-SGP; RV1 Phua 2009-AS; RV1 Ruiz-Palac 06 LA/EU; RV1 Salinas 2005-LA; RV1 Vesikari 2004a-FIN; RV1 Vesikari 2004b-FIN; RV1 Vesikari 2011-FIN

[6] These trials were not designed to detect an effect on mortality

TABLE 2: EFFECTIVENESS OF RV1 COMPARED TO PLACEBO FOR PREVENTING ROTAVIRUS DIARRHOEA IN HIGH-MORTALITY COUNTRIES (WHO STRATA D&E) CONSIDERING THE FOLLOWING OUTCOMES: A): SEVERE ROTAVIRUS DIARRHOEA; B) SEVERE EPISODES OF ALL-CAUSE DIARRHOEA; C) ALL-CAUSE DEATH[7]

Table 2, Outcome A: Severe rotavirus diarrhoea episodes (follow up: up to 2 years)

PICO Question: WHAT IS THE EFFECT OF RV1 COMPARED TO PLACEBO FOR PREVENTING SEVERE ROTAVIRUS DIARRHOEA IN HIGH-MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		1 RCT (2764 participants)[8]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	serious[9]	-1
		Imprecision	none	0
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR: 0.58 (0.42-0.79)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			Further research may change the estimate of effect
	Conclusion			We are moderately confident that use of RV1 in high mortality countries reduces the rate of severe rotavirus diarrhoea

[7] Adapted from Soares-Weiser K, MacLehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD008521. DOI: 10.1002/14651858.CD008521.pub3.

[8] RV1 Madhi 2010-AF

[9] Trials were conducted in Malawi and South Africa: generalization to high-mortality countries is difficult

Table 2, Outcome B: Severe all-cause diarrhoea episodes (follow up: up to 2 years)

PICO Question: WHAT IS THE EFFECT OF RV1 COMPARED TO PLACEBO FOR PREVENTING SEVERE ALL-CAUSE DIARRHOEA IN HIGH-MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		1 RCT (2764 participants)[10]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	serious[11]	-1
		Imprecision	none	0
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR 0.82 (0.71-0.95)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			Further research may change the estimate of effect
	Conclusion			We are moderately confident that use of RV1 in high mortality countries reduces the rate of severe all-cause diarrhoea

[10] RV1 Madhi 2010-AF

[11] Trials were conducted in Malawi and South Africa: generalization to high-mortality countries is difficult

Table No 2: Outcome C: All-cause death (follow-up from 2 months to 2 years)

PICO Question: WHAT IS THE EFFECT OF RV1 COMPARED TO PLACEBO FOR PREVENTING ALL-CAUSE DEATH IN HIGH-MORTALITY COUNTRIES				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		7 RCTs (7481 participants)[12]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	none	0
		Imprecision	very serious [13]	-2
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR: 0.88 (0.64 to 1.22)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Further research is likely to change the estimate of effect.
	Conclusion			We are not certain about the effect of use of RV1 on all-cause death in high mortality countries

[12] RV1 GSK (033)2007-LA; RV1 Madhi 2010-AF; RV1 Narang 2009-IND; RV1 Steele 2008-ZAF; RV1 Steele 2010 a-ZAF; RV1 Steele 2010b-ZAF; RV1 Zaman 2009-BGD

[13] These trials were not designed to detect an effect on mortality.

Table 3: EFFECTIVENESS OF RV5 COMPARED TO PLACEBO FOR PREVENTING ROTAVIRUS DIARRHOEA IN LOW-MORTALITY COUNTRIES CONSIDERING THE FOLLOWING OUTCOMES: A): SEVERE ROTAVIRUS DIARRHOEA; B) SEVERE EPISODES OF ALL-CAUSE DIARRHOEA; C) ALL-CAUSE DEATH [14]

Table 3, Outcome A-Severe rotavirus diarrhoea, (follow-up: up to 2 years)

PICO Question: WHAT IS THE EFFECT OF RV5 COMPARED TO PLACEBO FOR PREVENTING SEVERE ROTAVIRUS DIARRHOEA IN LOW MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		3 RCTs (2344 participants)[15]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	none	0
		Imprecision	serious [16]	-1
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR: 0.18 (0.07-0.5)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			Further research may change the estimate of effect
	Conclusion			We are moderately confident that use of RV5 in low mortality countries reduces the rate of severe rotavirus diarrhoea

[14] Adapted from Soares-Weiser K, MacLehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD008521. DOI: 10.1002/14651858.CD008521.pub3.

[15] RV5 Clark 2004-USA; RV5 NCT 007 18237 2010-JPN; Vesikari-2006-INT

[16] The total number of events was very low.

Table No 3, Outcome B: Severe all-cause diarrhoea episodes-(follow up: up to 2 years)

PICO Question: WHAT IS THE EFFECT OF RV5 COMPARED TO PLACEBO FOR PREVENTING SEVERE EPISODES OF ALL-CAUSE DIARRHOEA IN LOW MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		1 RCT (1029 participants)[17]	4
	Factors decreasing confidence	Limitation in study design	serious[18]	-1
		Inconsistency	none	0
		Indirectness	none serious[19]	0
		Imprecision	serious[20]	-1
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR: 0.04 (0-0.7)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Further research is very likely to have an important impact on our confidence in the estimate of effect
	Conclusion			We are not certain whether the use of RV5 in low mortality countries has any effect on severe all-cause diarrhoea

[17] RV5 Vesikari 2006a-FIN

[18] The included study did not report incomplete outcome data sufficiently.

[19] Although the study was carried out in only one country (Finland) it was not downgraded for serious indirectness as it was considered representative of low-mortality countries

[20] The number of events was very low.

Table No 3, Outcome C: All-cause death (follow up-2 months to 2 years)

PICO Question: WHAT IS THE EFFECT OF RV5 COMPARED TO PLACEBO FOR PREVENTING ALL-CAUSE DEATH IN LOW-MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		8 RCTs (73,603 participants)[21]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	none	0
		Imprecision	very serious [22]	-2
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR 1.18 (0.67-2.08)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Further research is very likely to have an important impact on our confidence in the estimate of effect.
	Conclusion			We are not certain whether the use of RV5 in low mortality countries has any effect on all-cause death

[21] RV5 Block 2007-EU/USA; RV5 Ciarlet 2009-EU; RV5 Merck (009) 2005-USA; RV5 NCT00718237-JPN; RV5 NCT00953056 2010-CHN; RV5 Vesikari 2006a-FIN; RV5 Vesikari 2006-INT

[22] These trials were not designed to detect an effect on mortality.

Table No 4: EFFECTIVENESS OF RV5COMPARED TO PLACEBO FOR PREVENTING ROTAVIRUS DIARRHOEA IN HIGH-MORTALITY COUNTRIES CONSIDERING THE FOLLOWING OUTCOMES: A): SEVERE ROTAVIRUS DIARRHOEA; B) SEVERE EPISODES OF ALL-CAUSE DIARRHOEA; C) ALL-CAUSE DEATH[23]

Table 4, Outcome A: Severe rotavirus diarrhoea episodes (follow up: up to 2 years).

PICO Question: WHAT IS THE EFFECT OF RV5 COMPARED TO PLACEBO FOR PREVENTING SEVERE ROTAVIRUS DIARRHOEA IN HIGH-MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCTs (5885 participants)[24]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	none	0
		Imprecision	none	0
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR: 0.59 (0.43 to 0.82)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			Further research is very unlikely to change our confidence in the estimate of effect
	Conclusion			We are confident that use of RV5 in high mortality countries reduces the rate of severe rotavirus diarrhoea

[23] Adapted from Soares-Weiser K, MacLehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD008521. DOI: 10.1002/14651858.CD008521.pub3.

[24] RV5 Armah 2010-AF; RV5 Zaman 2010-AS

Table No 4, Outcome B: Severe all-cause diarrhoea, (follow-up: up to 2 years).

PICO Question: WHAT IS THE EFFECT OF RV5 COMPARED TO PLACEBO FOR PREVENTING SEVERE ALL-CAUSE DIARRHOEA IN HIGH-MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCTs (5977 participants)[25]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	none	0
		Imprecision	none	0
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR: 0.85 (0.75-0.98)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			Further research is very unlikely to change our confidence in the estimate of effect
	Conclusion			We are confident that use of RV5 in high mortality countries reduces the rate of severe all-cause diarrhoea

[25] RV5 Armah 2010-AF; RV5 Zaman 2010-AS

Table No 4: Outcome C: All-cause death (follow up-2 months to 2 years)

PICO Question: WHAT IS THE EFFECT OF RV1 COMPARED TO PLACEBO FOR PREVENTING ALL-CAUSE DEATH IN HIGH-MORTALITY COUNTRIES?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCTs (6604 participants)[26]	4
	Factors decreasing confidence	Limitation in study design	none	0
		Inconsistency	none	0
		Indirectness	none	0
		Imprecision	very serious[27]	-2
		Publication bias	none detected	0
	Factors increasing confidence	Strength of association/ large effect	RR 0.93 (0.69-1.25)	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Further research is likely to change the estimate of effect
	Conclusion			We are not certain whether the use of RV5 in low mortality countries has any effect on all-cause death

[26] RV5 Armah 2010-AF; RV5 Zaman 2010-AS

[27] These trials were not designed to detect an effect on mortality