

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

Methods and Statistical Analysis

Study selection

Two reviewers (Sun ZW and Fu Y) independently screened the title, abstract and keywords of each EndNote record for relevance, and assessed in detail the full text of manuscripts for inclusion, with a third reviewer (Lu HL) consulted when necessary. Initial literature retrieval until July 1, 2018 produced 3998 articles and 241 full-text articles were assessed for eligibility. Updated research until July 1, 2020 produced 1131 articles and 50 full-text articles were assessed for eligibility. Seventeen studies were further identified from updated literature retrieval and 121 studies were finally included.

Data collection process

We developed a standardized data extraction form including study methods, field-work dates, population sampled, recruitment site, sample size of vaccine and control groups, diagnostic assays used, vaccine type and title, vaccination schedule and rate of rotavirus cases, serious adverse events and seropositivity. Two reviewers (Sun ZW and Fu Y) independently extracted data and methodological quality of included trails and then rechecked the data with each other. For 10% of included studies, data were double extracted by a third author (Lu HL) to check for accuracy.

eTable 1. Included Criteria During Selection Process

1. Study design: Randomized controlled trials, Case-control studies or Cohort studies;
2. An original report of vaccine efficacy or effectiveness against rotavirus disease or assessing the safety or immunogenicity of rotavirus vaccine;
3. The efficacy, effectiveness, safety and immunogenicity of rotavirus vaccine were reported by vaccine types;
4. Rotavirus vaccines researched were licensed in global or regional market, including RV1, RV5, Rotavac, BRV-PV and LLR;
5. A sample size of at least 100 participants;
6. At least one full rotavirus season was included;
7. Enrolled population were normal children, younger than 5 years;
8. Clear reporting of the numbers of rotavirus cases and vaccination status;
9. Infants enrolled in RCTs should receive oral vaccines according to recommended schedules and recommended concentrations;
10. Rotavirus gastroenteritis should be confirmed by EIA or ELISA and genotyped by reverse transcription PCR.

eTable 2. The Criteria for grading methodological quality

Assessment quality of RCTs in the <i>Cochrane Reviewers' Handbook</i>	
Low quality	If either randomization or allocation concealment was assessed at high risk of bias, regardless of the risk of other items.
High quality	When both randomization and allocation concealment were assessed as a low risk of bias, and all other items were assessed at low or unclear risk of bias.
Moderate quality	If a trial did not meet criteria for high or low quality.
Assessment quality of observational studies with the Newcastle-Ottawa Scales (NOS).	
Low risk of bias	Up to one item was judged inadequate in a study.
Medium risk of bias	Up to three items were judged inadequate in a study.
High risk of bias	More than three items were judged inadequate in a study.
Very high risk of bias	There was no description of methods.

eTable 3. The basis for grouping studies in sub-analysis

The groups in sub-analysis	Contents in each stratification
Economic development	
High-income countries	GNI per capita \geq US\$12,745
Middle-income countries	GNI per capita from US\$1,046 to US\$12,744
Low-income countries	GNI per capita \leq US\$1,045
Rotavirus strain	
Homotypic strain	Both G-type and P-type antigens of the circulating strain were in the vaccine
Partly heterotypic strain	Either the G-type or the P-type antigen of the circulating strain was in the vaccine
Fully heterotypic strain	Neither G-type nor P-type antigens of the circulating strain were in the vaccine
Single-antigen vaccine type	Single G-type or P-type antigens of the circulating strain was in the vaccine, eg, G1, G2, G3, G4, and P8
Single-antigen non-vaccine type	Single G-type or P-type antigens of the strain was not in the vaccine, eg, all other G-types or P-types
Duration of follow-up	
First year follow-up	The follow-up time was up to the first year or the first rotavirus season after vaccination
Second year follow-up	The follow-up time was up to the second year or the second rotavirus season after vaccination
Two years follow-up	The follow-up time was up to two years or two rotavirus seasons after vaccination

eTable 4. Characteristics of the Included RCTs, Case-control and Cohort studies

RCTs									
Countries or Regions	Source	Mean Age At Dose 1	Vaccine Group / Placebo Group			Vaccination Schedule (Titer/Dose)	Follow-up Duration	Main Genotype	Quality
			Male (%)	Breast Feeding (%)	Treatment				
The USA	Bernstein et al,1999 ¹	12 wk	54/53	48/56	RV1(108/107)	≥10 ⁵ FFU/2 doses	1 rotavirus season	NA	M
	Dennehy et al, 2005 ²	NA	NA	No restrict	RV1(209/108)	10 ^{6.4} FFU/2 doses	1 rotavirus season	NA	H
	Grant et al, 2012 ³	9.8 wk	51/51	No restrict	RV5(512/496)	≥10 ⁷ FFU/3 doses	1 rotavirus season	NA	H
Europe (6 countries)	Vesikari et al, 2007 ⁴	11.5 wk	53/54	NA	RV1(2646/1348)	10 ^{6.5} FFU/2 dose	2 rotavirus seasons	G1P[8],G2P[4],G9P[8]	H
	Vesikaria et al, 2010 ⁵	10.4 wk	53/54	NA	RV1(914/490)	≥10 ⁶ FFU/2 dose	1 rotavirus season	NA	H
Europe (5)	Vesikari et al, 2009 ⁶	9.8 wk	51/51	No restrict	RV5(15278/15217)	6.7-12.4×10 ⁷ FFU/3 doses	2 rotavirus seasons	G1,G3,G4,G9	H
Finland	Vesikari et al, 2006 ⁷	NA	NA	No restrict	RV5(328/322)	8×10 ⁶ FFU/3 doses	3 rotavirus seasons	NA	L
	Vesikaria et al, 2011 ⁸	NA	NA	NA	RV1(100/50)	≥10 ⁶ FFU/2 dose	2 rotavirus seasons	NA	M
Japan	Kawamura et al, 2011 ⁹	7.7 wk	NA	NA	RV1(508/257)	≥10 ⁶ FFU/2 doses	2 rotavirus seasons	NA	L
	Iwata et al,2013 ¹⁰	8 wk	54/52	NA	RV5(380/381)	NA	2 rotavirus seasons	NA	H
Korea	Kim et al, 2008 ¹¹	9 wk	60/52	No restrict	RV5(115/63)	6.9×10 ⁷ -8.6×10 ⁷ FFU/ 3 does	2 rotavirus seasons	NA	L
	Kim et al, 2012 ¹²	8.8 wk	55/55	NA	RV1(508/176)	≥10 ⁶ FFU/2 doses	1 rotavirus season	NA	H
Singapore	Phua et al, 2009 ¹³	11.6 wk	51/51	NA	RV1(5359/5349)	≥10 ⁶ FFU/2 doses	2 rotavirus seasons	G1,G3,G9	H
Hong Kong	Phua et al, 2012 ¹⁴	11.6 wk	51/51	NA	RV1(4359/4328)	≥10 ⁶ FFU/2 doses	3 rotavirus seasons	G1P[8],G3P[8],G9P[8]	H
Taiwan	Phua et al, 2016 ¹⁵	13.3 wk	50/50	NA	RV1(3274/3268)	NA	3 rotavirus seasons	G1P[8],G3P[8],G9P[8]	H
	Phua et al, 2005 ¹⁶	13.3 wk	50/50	NA	RV1 (639/642)	10 ^{6.1} FFU/2 doses	1 rotavirus season	NA	L
China	Li et al, 2014 ¹⁷	9.6 wk	NA	NA	RV1(1666/1667)	≥10 ⁶ FFU/2 doses	2 rotavirus seasons	G1P[8],G2P[4]	M
	Li et al, 2016 ¹⁸	10 wk	NA	NA	RV1(459/459)	≥10 ⁶ FFU/2 doses	2 rotavirus seasons	NA	M
China (Hong Kong)	Lau et al, 2013 ¹⁹	11.6 wk	51/51	NA	RV1(1513/1512)	≥10 ⁶ FFU/2 doses	2 rotavirus seasons	G1,G3,G9	H
China (Guangxi)	Mo et al, 2017 ²⁰	8.5 wk	51/53	NA	RV5(2020/2020)	2-2.8×10 ⁶ FFU/3 doses	2 rotavirus seasons	G1,G9,G3,G4	M
China (Guangxi)	Mo et al, 2019 ²¹	8.5 wk	51/53	NA	RV5(2020/2020)	2-2.8×10 ⁶ FFU/3 doses	2 rotavirus seasons	NA	M
China (Taiwan)	Chang et al, 2008 ²²	NA	NA	NA	RV5(96/93)	6.5×10 ⁷ -1.2×10 ⁸ FFU/3 doses	2 rotavirus seasons	NA	L
China (Henan)	Xia et al, 2020 ²³	9.8 wk	50/50	NA	LLR (4993/4992)	TCID ₅₀ /ml titers/3 doses	2 rotavirus seasons	G1,G2,G3,G4,G9	H
Bangladesh	Colgate et al, 2016 ²⁴	10 wk	52/53	50/54	RV1(350350)	NA	1 rotavirus season	NA	H
	Zaman et al, 2009 ²⁵	6.1 wk	53/54	NA	RV1(196/98)	10 ^{6.5} FFU/2 doses	1 rotavirus season	NA	L
Bangladesh	Zaman et al, 2010 ²⁶	9 wk	54/49	No restrict	RV5(568/568)	2×10 ⁷ FFU/3 doses	≥3 rotavirus seasons	NA	H
Vietnam	Anh et al, 2011 ²⁷	8.7 wk	NA	NA	RV1(297/78)	≥10 ⁶ FFU/2 doses	1 rotavirus season	NA	H
Philippines		8.5 wk			RV1(300/75)				
India	Narang et al, 2009 ²⁸	8.7 wk	49/57	NA	RV1(182/181)	≥10 ⁶ FFU/2 doses	2 rotavirus seasons	NA	M
	Bhandari et al, 2009 ²⁹	8 wk	55/50	NA	Rotavac(92/90)	≥10 ⁵ FFU/3 doses	2 rotavirus seasons	NA	H
	John et al, 2014 ³⁰	NA	NA	No restrict	Rotavac(4532/2267)	NA	2 rotavirus seasons	NA	M
	Bhandari et al, 2014 ³¹	6.8 wk	51/51	No restrict	Rotavac(4532/2267)	≥10 ⁵ FFU/3 doses	2 rotavirus seasons	NA	H
	Kulkarniet al,2017 ³²	6 wk	50/51	No restrict	BRV-PV(3749/3751)	≥10 ^{5.6} FFU/3 doses	2 rotavirus seasons	NA	M
Latin America (6)	Tregnaghi et al, 2011 ³³	8.6 wk	NA	NA	RV1 (4376/2192)	≥10 ⁶ FFU/2 doses	1 rotavirus season	G9P[8],G2P[4]	M
Latin America (10)	Linhares et al, 2008 ³⁴	8.3 wk	51/51	NA	RV1(10159/10010)	10 ^{6.5} FFU/2 doses	2 rotavirus seasons	G1P[8],G2P[4],G9P[8]	H
Brazil, Mexico, Venezuela	Salinas et al, 2005 ³⁵	8.3 wk	53/50	NA	RV1 (540/537)	10 ^{5.8} FFU/2 doses	1 rotavirus season	G1,G9,G2	H
Mexico	Ruiz-Palacios et al, 2007 ³⁶	7.7 wk	55/57	50/52	RV1 (102/101)	10 ^{5.8} FFU/2 doses	1 rotavirus season	G1,G2,G9	H
Brazil	Justino et al, 2012 ³⁷	9.8 wk	50/53	NA	RV1(328/325)	10 ^{6.5} FFU/2 doses	2 rotavirus seasons	G1P[8],G9P[8]	H
Jamaica	Christie et al, 2010 ³⁸	7.8 wk	53/50	NA	RV5(907/898)	6.7-12.4×10 ⁷ FFU/3 doses	3 rotavirus seasons	NA	H
Niger	Isanaka et al, 2017 ³⁹	6.8 wk	50/49	No restrict	BRV-PV(2044/2047)	>10 ^{5.6} FFU/3 doses	2 rotavirus seasons	NA	H

	Coldiron et al, 2018 ⁴⁰	6 wk	50/49	No restrict	BRV-PV(2044/2047)	>10 ^{5.6} FFU/3 doses	2 rotavirus seasons	NA	H
South Africa, Malawi	Madhi et al, 2010 ⁴¹	6.4 wk	50/49	No restrict	RV1(3298/1641)	10 ^{6.5} FFU/2 doses	1 rotavirus season	G1P[8]	H
	Steele et al, 2012 ⁴²	6.4 wk	50/49	No restrict	RV1(3298/1641)	10 ^{6.5} FFU/2 doses	2 rotavirus seasons	G1,G12,G8,P[8]	H
South Africa	Steele et al, 2010 ⁴³	6 wk	NA	NA	RV1(190/96)	≥10 ⁶ FFU/2 doses	1 rotavirus season	NA	L
Malawi	Cunliffe et al, 2012 ⁴⁴	6.5 wk	49/50	No restrict	RV1(1182/591)	10 ^{6.5} FFU/2 doses	2 rotavirus seasons	G12P[6],G9P[8],G1P[8]	H
Colombia	Rojas et al, 2007 ⁴⁵	8.6 wk	46/47	NA	RV1(159/160)	10 ^{6.7} FFU/2 doses	1 rotavirus season	NA	L
Ghana	Armah et al, 2010 ⁴⁶	8.4 wk	49/49	No restrict	RV5(1098/1102)	2x10 ⁷ FFU/3 doses	2 rotavirus seasons	NA	H
Kenya		7.3 wk	48/49		RV5(656/652)				
Mali		6.9 wk	53/51		RV5(979/981)				
Ghana,Kenya, Mali	Tapia et al, 2012 ⁴⁷	6 wk		No restrict	RV5(2733/2735)	2x10 ⁷ FFU/3 doses	2 rotavirus seasons	G1P[8],G2P[4],G1P[6],G2P[6]	H
Mali	Sow et al, 2012 ⁴⁸	6.9 wk	53/51	No restrict	RV5(979/981)	2x10 ⁷ FFU/3 doses	2 rotavirus seasons	G1P[8],G2P[6],G1P[6],G2P[4]	H
Kenya	Laserson et al, 2012 ⁴⁹	6 wk	NA	NA	RV5(649/643)	2x10 ⁷ FFU/3 doses	2 rotavirus seasons	NA	H
Bangui	Georges et al, 1991 ⁵⁰	3m	NA	NA	RV5(230/232)	1x10 ⁷ FFU/3 doses	1 rotavirus season	NA	L
Finland, Latin America (11)	Ruiz-Palacios et al, 2006 ⁵¹	8.3 wk	51/51	NA	RV1(31673/31552)	10 ^{6.5} FFU/2 doses	1 rotavirus season	G1P[8],G2P[4],G9P[8]	H
Africa(Ghana,Kenya,Mali), Asia(Bangladesh, Vietnam)	Breiman et al, 2012 ⁵²	6 wk	NA	No restrict	RV5(3751/3753)	2x10 ⁷ FFU/3 doses	2 rotavirus seasons	NA	H
America, Finland	Block et al, 2007 ⁵³	10 wk	53/51	NA	RV5(651/661)	10 ⁷ FFU/3 doses	2 rotavirus seasons	NA	H
America, Europe (5), Latin American/Caribbean region (5)	Vesikari et al, 2006 ⁵⁴	9.8 wk	51/51	No restrict	RV5(34644/34630)	6.7-12.4x10 ⁷ FFU/3 doses	2 rotavirus seasons	G1,G3,G4,G9	H
	Goveia et al, 2008 ⁵⁵	9.8 wk	51/51	No restrict	RV5(34644/34630)	6.7-12.4x10 ⁷ FFU/3 doses	2 rotavirus seasons	G1,G3,G4,G9	H
	Dennehy et al, 2007 ⁵⁶	9.8 wk	51/51	No restrict	RV5(36271/35671)	≥10 ⁷ FFU/3 doses	1 rotavirus season	NA	H
Europe United States Latin America	Vesikari et al, 2007 ⁵⁷	9.8 wk	51/51	No restrict	RV5(15057/15018) RV5(16170/16178) RV5(2713/2713)	6.7-12.4x10 ⁷ FFU/3 doses	2 rotavirus seasons	NA	H

Case control studies

Countries or Regions	Source	Case Group / Control Group			Type of controls	Vaccination Schedule (Case/Control)	Total Population (Case/Control)	Main Genotype	Risk	
		Mean Age	Male (%)	Breast Feeding (%)						
The USA	Cortese et al, 2013 ⁵⁸	NA	NA	No restrict	HRV(-) in hospital Neighborhood	RV1 full (22/101) RV5 full (6/34) RV1 full (19/644) RV5 full (4/253)	95/140 89/1302	G1P[8],G2P[4],G12P[8],G3P[8]	H	
	Immergluck et al, 2016 ⁵⁹	NA	73/55	75/73	HRV(-) in hospital	RV1 full (16/48) RV1 partial (3/4) RV5 full (22/34) RV5 partial (5/10)	92/134	G12P[8],G3P[8]	L	
	Staat et al,2011 ⁶⁰	13m/12m	52/53	NA	Nondiarrhea controls in hospital	HRV(-) in hospital	RV5 full (16/87) RV5 partial (16/91)	159/329	G3,G9,G1	L
						RV5 full (17/195) RV5 partial (17/168)	183/675			
	Tate et al, 2013 ⁶¹	23m/12m	NA	70/63 70/57	Nondiarrhea controls in hospital	HRV(-) in hospital	RV5 full (22/164) RV5 partial (17/129)	158/490	NA	H
						RV5 full (22/187) RV5 partial (17/127)	158/500			
	Donauer et al, 2013 ⁶²	NA	45/52	50/60	Nondiarrhea controls in hospital	Neighborhood	RV5 full (2/329) RV5 partial (8/165)	76/743	G1P[8],G12P[8],G2P[4],G8P[9]	H
HRV(-) in hospital						RV5 full (2/15) RV5 partial (8/47)	76/179			
RV5 full (2/27) RV5 partial (8/71)						76/288				
Boom et al, 2010 ⁶³	17m/10m	66/58	NA	Nondiarrhea controls in hospital	HRV(-) in hospital	RV5 full (5/32) RV5 partial (7/29)	79/108	G3P[8],G1P[8]	L	
					RV5 full (5/44) RV5 partial(7/71)	79/206				
Cortese et al, 2011 ⁶⁴	NA	NA	NA	HRV(-) in hospital Neighborhood	RV5 full (28/163) RV5 full (23/810)	402/825	NA	L		
Quebec	Doll et al, 2015 ⁶⁵	16.6m/12.6m	38/56	NA	HRV(-) in hospital	RV1 partial (1/26) RV1 full (7/74)	32/342	NA	H	
El Salvador	Palma et al, 2010 ⁶⁶	10 m/10m	64/50	91/93	Neighborhood	RV1 full (152/617) RV1 partial (72/199)	323/969	NA	L	
Belgium	Braeckman et al, 2012 ⁶⁷	13m/12.6m	51/54	2/4	Nondiarrhea controls in hospital	RV1 full (66/165) RV1 partial (70/94)	215/276	G1P[8],G2P[4]	L	
	Matthijnsens et al, 2014 ⁶⁸	NA	NA	NA	Nondiarrhea controls in hospital	RV1 full (70/179) RV1 partial (88/78)	248/276	G2P[4],G1P[8],G4P[8],G3P[8]	L	
Spain	Castilla et al,2012 ⁶⁹	NA	54/56	NA	HRV(-) in hospital	RV1 full (19/459) RV1 partial(2/67)	756/6036	NA	M	

						RV5 full (15/390) RV5 partial (9/168)			
England	Walker et al, 2019 ⁷⁰	19.4w/20.4w	53.7/53.5	NA	HRV(-) in hospital	RV1 full (1126/653) RV1 partial(186/130)	1702/956	NA	M
Germany	Oberle et al, 2020 ⁷¹	7.7m/7.8m	70.7/68.4	NA	Neighborhood	RV1 partial(35/78) RV5 partial(21/48)	116/272	NA	L
Moldova	Gheorghita et al, 2016 ⁷²	11.6m/11.6m	51/57	NA	HRV(-) in hospital	RV1 full (14/348) RV1 partial (4/51)	100/852	NA	L
Australia	Snelling et al, 2009 ⁷³	NA	NA	NA	HRV(-) in hospital	RV1 full (11/72) RV1 partial (10/48)	42/166	G9P[8],G1P[8]	L
	Carlin et al, 2013 ⁷⁴	<12m	NA	NA	Neighborhood	RV1 partial (120/1078) RV5 partial (135/1186)	137/1319 164/1453	NA	M
	Maguire et al, 2019 ⁷⁵	25m	NA	NA	Neighborhood	RV1 full (1977/24902) RV1 partial (184/1808)	2931/29273	NA	H
Japan	Araki et al, 2018 ⁷⁶	19/15m	55/54	30/44	HRV(-) in hospital	RV1 full (36/226) RV1 full (27/179)	487/925	G1P[8],G9P[8],G2P[4]	M
	Araki et al, 2018 ⁷⁷	16m/13m	53/56	NA	HRV(-) in hospital	RV1 full (3/41) RV5 full (0/38)	64/260	NA	M
			53/48		Nondiarrhea controls in hospital	RV1 full (23/121) RV5 full (0/53)	64/589		
Philippines	Lopez et al, 2018 ⁷⁸	11m/11m	57/59	NA	HRV(-) in hospital	RV1 full (92/233) RV1 partial (20/44)	203/397	NA	M
Israel	Muhsen et al, 2018 ⁷⁹	NA	55/53	NA	HRV(-) in hospital	RV5 full (46/363) RV5 partial (26/203)	98/628	G1P[8],G3P[8], G9P[8],G2P[4]	L
Uzbekistan	Eraliev et al, 2020 ⁸⁰	≥6m	NA		HRV(-) in hospital	RV1 full (76/400)	102/499	NA	H
China (Taiwan)	Chang et al, 2014 ⁸¹	20.5m/18.2m	NA	NA	HRV(-) in hospital	RV1 full (3/121) RV1 partial (0/6) RV5 full (0/82) RV5 partial (0/5)	184/904	G1P[8],G2P[4],G3P[8], G9P[8]	M
		20.5m/19m			Nondiarrhea controls in hospital	RV1 full (3/154) RV1 partial (0/4) RV5 full (0/90) RV5 partial (0/3)	184/909		
China (Guangzhou)	Fu et al,2007 ⁸²	17.1m/15.7m	NA	NA	HRV(-) in hospital	LLR full (0/6) LLR partial (90/186)	838/838	NA	H
		13.3m/12.5m	65/65	NA	Nondiarrhea controls in hospital	LLR full (9/19) LLR partial(383/587)	3130/3607	NA	L
China (Hebei)	Zhen et al, 2015 ⁸⁴	NA	NA	NA	HRV(-) in hospital	LLR	305/1220	G3,G1,G9	M
China (Beijing)	Li et al, 2019 ⁸⁵	NA	65/59	NA	HRV(-) in hospital	LLR	598/1766	G9,G3,G2	M
Nicaragua	Patel et al, 2009 ⁸⁶	10m/8m	56/52	92/92	Neighborhood	RV5 full (42/137) RV5 partial(116/349)	285/840	NA	L
			56/54		HRV(-) in hospital	RV5 full (42/120) RV5 partial(116/262)	285/690		
	Mast et al, 2011 ⁸⁷	14m/14m	59/56	93/93	HRV(-) in hospital	RV5 full (241/711)	502/1894	G3,G9,P[1],P[8]	M
			59/52	93/94	Neighborhood	RV5 full (241/812)	502/1685		
	Patel et al, 2012 ⁸⁸	14m/11m	54/58	92/94	HRV(-) in hospital	RV5 full (773/3097)	1016/4930	NA	M
		14m/14m	54/52	92/95	Nondiarrhea controls in hospital	RV5 full (773/3914)	1016/5627		
Guatemala	Gastañaduy et al, 2016 ⁸⁹	12m/14m	66/53	89/90	Nondiarrhea controls in hospital	RV1 full (41/175) RV5 full (19/78)	213/657	G1P[8]	M
		12m/11m	66/59	89/90	HRV(-) in hospital	RV1 full (41/90) RV5 full (19/27)	213/334		
Brazil	Correia et al, 2010 ⁹⁰	14m/12m	73/54	NA	HRV(-) in hospital	RV1 full (43/317)	70/484	G2P[4]	H
		14m/19m	73/58		Nondiarrhea controls in hospital	RV1 full(43/310)	70/416		
	Patel et al, 2013 ⁹¹	12m/12m	65/56	93/94	HRV(-) in hospital	RV1 full (208/510) RV1 partial(100/131)	400/718	G9P[8],G3P[8],G2P[4], G9P[6]	L
			65/54	93/97	Nondiarrhea controls in hospital	RV1 full (208/857) RV1 partial(100/226)	400/1200		
	Ichihara et al, 2014 ⁹²	14m/14m	NA	NA	Nondiarrhea controls in hospital	RV1 full (115/1481) RV1 partial (33/279)	215/1961	G2P[4],G1P[8]	M
	Justino et al, 2011 ⁹³	16m/18m	51/53	NA	Nondiarrhea controls in hospital	RV1 full (289/308) RV1 partial (77/79)	538/507	G2P[4],G1P[8],G2P[6], G12P[6]	L
		16m/17m	51/55		Neighborhood	RV1 full (289/256) RV1 partial (77/39)	538/346		
Brazil	Patel et al, 2011 ⁹⁴	5.5m	NA	NA	Neighborhood	RV1 (312/1264)	330/1311	NA	L
Mexico		5.2m				RV1 (260/672)	285/739		
Bolivia	Pringle et al, 2016 ⁹⁵	13m/14m	64/61	97/96	HRV(-) in hospital	RV1 full (264/345) RV1 partial (60/57)	356/420	G9,P[8],G3,P[6]	L
Colombia	Cotes-Cantillo et al, 2014 ⁹⁶	17m/15m	61/58	84/86	Nondiarrhea controls in hospital	RV1 full (143/670) RV1 partial (17/90)	173/801	NA	M
Zambia	Beres et al, 2016 ⁹⁷	8m/8m	49/50	NA	HRV(-) in hospital	RV1 full (70/238) RV1 partial (16/44)	144/458	NA	L
Malawi	Bar-Zeev et al, 2015 ⁹⁸	8.9m/9.4m	NA	91/92	HRV(-) in hospital	RV1 full (81/234) RV1 partial (9/30)	118/317	G2P[4],G1P[8],G12P[6], G2P[6]	L
		8.9m/8.8m		NA	Neighborhood	RV1 full (81/286) RV1 partial (9/42)	118/380		
South Africa	Groome et al, 2014 ⁹⁹	9m/10m	56/56	65/63	HRV(-) in hospital	RV1 full (278/856) RV1 partial(126/334)	540/1434	G12P[8],G2P[4],G1P[8], G9P[8]	L
		9m/8m	56/57	65/62	Nondiarrhea controls in hospital	RV1 full (278/697) RV1 partial(126/232)	540/1069		

	Groome et al, 2019 ¹⁰⁰	NA	NA	NA	Neighborhood	RV1	169/169	NA	H
Botswana	Gastañaduy et al, 2016 ¹⁰¹	9m/8m	52/57	47/55	HRV(-) in hospital	RV1 full (162/288) RV1 partial (37/51)	242/368	NA	H
	Mokomane et al, 2018 ¹⁰²	9m/8m	52/57	47/45	HRV(-) in hospital	RV1 full (121/288) RV1 partial (29/51)	242/368	NA	M
Ghana	Armah et al, 2016 ¹⁰³	11.3m/11.5m	52/60	99/98	HRV(-) in hospital	RV1 full (197/428) RV1 partial (0/9)	207/450	NA	L
Burkina Faso	Bonkougou et al, 2018 ¹⁰⁴	12m/10m	61/57	NA	HRV(-) in hospital	RV5 full (133/488) RV5 partial (12/44)	227/761	NA	L
Rwanda	Tate et al, 2016 ¹⁰⁵	15.5m/10m	56/63	NA	HRV(-) in hospital	RV5 full (5/49) RV5 partial (7/7)	48/152	NA	M
Zimbabwe	Mujuru et al, 2018 ¹⁰⁶	12m/13m	57/58	NA	HRV(-) in hospital	RV1 full (853/2527) RV1 partial (15/45)	903/2685	NA	M
Kenya	Khagayi et al, 2019 ¹⁰⁷	9.7m/9.8m	45/49	NA	HRV(-) in hospital	RV1 full (51/308) RV1 partial (7/41)	91/418	G1P[8],G2P[4]	M

Cohort studies

Countries or Regions	Source	Study design	Vaccinated Group / Unvaccinated Group			Vaccination Schedule	Follow-up time	Main Genotype	Risk
			Age (Mean)	Male (%)	Vaccinated (N)				
The USA	Wang et al, 2010 ¹⁰⁸	retrospective	7m/7m	51%/51%	RV5 (33140/26167)	3 doses	2 rotavirus seasons	NA	L
	Wang et al, 2013 ¹⁰⁹	prospective	2m/2m	51%/51%	RV5 (42306/28417) RV5 (43704/31810)	≥1 dose 2 doses	2 rotavirus seasons	NA	L
	Shui et al, 2012 ¹¹⁰	retrospective	4-34w	NA	RV5(309844/389026)	≥1 dose	30 days	NA	M
	Krishnarajah et al, 2017 ¹¹¹	prospective	NA	52%/53%	RV1(34928/182269) RV1 (8390/182269)	2 doses 1 dose	1 rotavirus season	NA	L
	Hoffman et al, 2017 ¹¹²	retrospective	NA	NA	RV1(57931/173384)	≥1 dose	59 days	NA	M
Canada (Quebec)	Gosselina et al, 2016 ¹¹³	prospective	NA	51%/52%	RV1 (4767/1239)	2 doses	2 years	NA	L
		retrospective		51%/51%	RV1 (266/1239) RV1 (4767/6436) RV1 (266/6436)	1 dose 2 doses 1 dose			
Poland	Budzyn et al, 2016 ¹¹⁴	retrospective	2.9y/2.6y	51%/51%	RV1 (303/303)	2 doses	5 years	NA	M
Spain	Pérez-Vilar et al, 2015 ¹¹⁵	retrospective	NA	52%/52%	RV1 (3604/96643) RV1 (24723/96643) RV5 (34865/96643) RV5 (10130/96643) RV5 (8563/96643)	2 doses 1 dose 3 doses 2 doses 1 dose	3 years	NA	L
France	Gagneur et al, 2011 ¹¹⁶	prospective	NA	NA	RV5 (1895/2102)	3 doses	2 years	NA	M
Israel	Muhsena et al, 2010 ¹¹⁷	prospective	NA	NA	RV1 (6870/18591) RV1 (716/18591)	2 doses 1 dose	2 rotavirus seasons	NA	L
Bangladesh	Zaman et al, 2017 ¹¹⁸	prospective	NA	NA	RV1 (5837/5267)	≥1 dose	2 years	G12P[8],G1P[8],G9P[8]	L
Thailand	Tharmaphornpilas et al, 2017 ¹¹⁹	prospective	NA	52%/50%	RV1 (3622/2472)	≥1 dose	2 years	NA	L
Brazil	Vieira et al, 2011 ¹²⁰	prospective	6.6m/15.3m	51%/49%	RV1 (222/222)	2 doses	2 years	G2P[4]	H
Malawi	Bar-Zeev et al, 2018 ¹²¹	prospective	NA	NA	RV1 (26086/1724) RV1 (563/1724)	2 doses 1 dose	1 year	NA	M
		retrospective			RV1 (26649/7690)	≥1 dose			

Table 5. Estimated Pooled Vaccine Protection in Cohort Studies

Study	Setting	Income	Vaccine	Vaccinated Dose	Cohort years	Study design	Incidence among vaccinated (N)	Incidence among unvaccinated (N)	RR (95% CI)
Hospitalisation for RVGE									
Tharmaphornpilas et al.2017	Thailand	UMIC	RV1	≥1 dose	2	prospective	10/3622	55/2472	0.124 (0.063, 0.243)
Gosselina et al.2016	Quebec (Canada)	HIC	RV1	2 doses	2	prospective	1/4767	1/1239	0.260 (0.063, 4.152)
				2 doses	2	retrospective	1/4767	21/6436	0.064 (0.063, 0.478)
				1 dose	2	prospective	1/266	1/1239	4.658 (2.063, 74.233)
				1 dose	2	retrospective	1/266	24/6436	1.008 (1.063, 7.424)
Krishnarajah et al.2017	the USA	HIC	RV1	2 doses	5	prospective	7/61035	526/370086	0.081 (0.063, 0.170)
				1 dose	5	prospective	3/14500	820/370086	0.093 (0.063, 0.290)
Pérez-Vilar et al.2015	Spain	HIC	RV1	2 doses	3	retrospective	20/21119	616/96643	0.149 (0.063, 0.232)
				1 dose	3	retrospective	3/24723	616/96643	0.019 (0.063, 0.059)
				RV5	3	retrospective	12/34865	616/96643	0.054 (0.063, 0.096)
				1 dose	3	retrospective	7/53558	616/96643	0.021 (0.063, 0.043)
				2 doses	3	retrospective	5/44995	616/96643	0.017 (0.063, 0.042)
Wang et al.2010	the USA	HIC	RV5	3 doses	2	prospective	0/33140	23/26167	0.017 (0.063, 0.277)
Wang et al.2013	the USA	HIC	RV5	1 dose	2	prospective	2/42306	11/28417	0.122 (0.063, 0.551)
				2 doses	2	prospective	1/43704	13/31810	0.056 (0.063, 0.428)
Gagneur et al.2011	France	HIC	RV5	3 doses	2	prospective	1/1895	47/2102	0.024 (0.063, 0.171)
Hospitalisation for AGE									
Tharmaphornpilas et al.2017	Thailand	UMIC	RV1	≥1 dose	2	prospective	203/3622	232/2472	0.597 (0.498, 0.716)
Gosselina et al. 2016	Quebec (Canada)	HIC	RV1	2 doses	2	prospective	20/4767	11/1239	0.473 (0.227, 0.984)
				2 doses	2	retrospective	20/4767	73/6436	0.370 (0.226, 0.606)
				1 dose	2	prospective	8/266	11/1239	3.388 (1.376, 8.341)
				1 dose	2	retrospective	8/266	87/6436	2.225 (1.090, 4.542)
Krishnarajah et al.2017	the USA	HIC	RV1	2 doses	5	prospective	729/61035	8209/370086	0.538 (0.499, 0.581)
				1 dose	5	prospective	248/14500	8209/370086	0.771 (0.680, 0.874)
Wang et al.2010	the USA	HIC	RV5	3 doses	2	prospective	87/33140	160/26167	0.429 (0.331, 0.557)
Wang et al.2013	the USA	HIC	RV5	1 dose	2	prospective	53/42306	63/28417	0.565 (0.392, 0.814)
				2 doses	2	prospective	78/43704	98/31810	0.579 (0.430, 0.780)
Pérez-Vilar et al.2015	Spain	HIC	RV1	≥1 dose	3	retrospective	230/24723	1552/96643	0.579 (0.505, 0.665)
				RV5	≥1 dose	3	retrospective	332/53558	1552/96643
Community consultations for RVGE									
Zaman et al.2017	Bangladesh	LMIC	RV1	≥1 dose	1	prospective	75/2464	135/2340	0.528 (0.400, 0.696)
		LMIC	RV1	≥1 dose	2	prospective	102/4116	172/3893	0.561 (0.441, 0.714)
Vieira et al.2011	Brazil	LIC	RV1	2 doses	2	prospective	10/180	6/147	1.361 (0.507, 3.657)
Dorota et al.2016	Poland	HIC	RV1	2 doses	5	retrospective	33/303	62/303	0.532 (0.360, 0.787)
Krishnarajah et al.2017	the USA	HIC	RV1	2 doses	1	prospective	11/34928	449/182269	0.128 (0.070, 0.232)
				1 dose	1	prospective	3/8390	449/182269	0.145 (0.047, 0.452)
				2 doses	5	prospective	17/61035	820/370086	0.126 (0.078, 0.203)
				1 dose	5	prospective	7/14500	820/370086	0.218 (0.104, 0.458)
Wang et al.2010	the USA	HIC	RV5	3 doses	2	prospective	1/33140	43/26167	0.018 (0.003, 0.133)
Wang et al.2013	the USA	HIC	RV5	1 dose	2	prospective	2/42306	18/28417	0.075 (0.017, 0.322)
				2 doses	2	prospective	5/43704	18/31810	0.202 (0.075, 0.545)
Community consultations for AGE									
Vieira et al.2011	Brazil	LIC	RV1	2 doses	1	prospective	193/222	187/222	1.032 (0.956, 1.114)
Muhsena et al.2010	Israel	HIC	RV1	2 doses	1	prospective	1605/6870	8801/18591	0.494 (0.472, 0.516)
				1 dose	1	prospective	153/716	8801/18591	0.451 (0.392, 0.520)
Krishnarajah et al.2017	the USA	HIC	RV1	2 doses	5	prospective	7336/61035	53019/370086	0.839 (0.820, 0.858)
				1 dose	5	prospective	1812/14500	53019/370086	0.872 (0.835, 0.911)
Wang et al.2010	the USA	HIC	RV5	3 doses	2	prospective	1408/33140	1537/26167	0.723 (0.674, 0.776)
Wang et al.2013	the USA	HIC	RV5	1 dose	2	prospective	704/42306	584/28417	0.810 (0.726, 0.903)
				2 doses	2	prospective	852/43704	945/31810	0.656 (0.599, 0.719)
Getachew et al.2018	the USA	HIC	RV1	≥1 dose	5	retrospective	9192/10000	9818/10000	0.936 (0.930, 0.942)
				RV5	≥1 dose	5	retrospective	8205/10000	8474/10000
Severe RVGE									
Zaman et al.2017	Bangladesh	LMIC	RV1	≥1 dose	1	prospective	53/2472	101/2351	0.499 (0.360, 0.693)
		LMIC	RV1	≥1 dose	2	prospective	75/4136	130/3919	16.625 (13.248, 20.862)
Vieira et al.2011	Brazil	LIC	RV1	2 doses	2	prospective	5/180	4/147	1.021 (0.279, 3.733)
Diarrhoea-associated death									
Bar-Zeev et al.2018	Malawi	LIC	RV1	2 doses	1	prospective	91/26086	10/1724	0.601 (0.314, 1.153)
				1 dose	1	prospective	7/563	10/1724	2.144 (0.820, 5.605)
				2 doses	1	retrospective	91/26086	44/7690	0.610 (0.426, 0.873)
				1 dose	1	retrospective	7/563	44/7690	2.173 (0.983, 4.802)

eTable 6. Estimated Pooled Vaccine Protection against Severe RVGE Stratified by Income Development at Different Follow-up Times

Studies	Countries and regions	Income	Vaccine(n/N)	Placebo(n/N)	RR (95% CI)	P	I ²
RV1							
First year follow-up							
Bernstein DI (1999)	The USA	HIC	2/108	9/107	0.220 (0.049, 0.995)		
Phua KB (2012)	Singapore, Hong Kong, Taiwan	HIC	0/5263	15/5256	0.032 (0.002, 0.538)		
Vesikari T (2007)	Europe (6)	HIC	5/2572	60/1302	0.042 (0.017, 0.105)		
Subtotal-HIC					0.071 (0.021, 0.238)	<0.001	45.7%
Li RC (2014)	China	UMIC	8/1575	32/1573	0.250 (0.115, 0.540)		
Ruiz-Palacios GM (2007)	Mexico	UMIC	0/78	7/87	0.074 (0.004, 1.279)		
Ruiz-Palacios GM (2006)	Finland, Latin America (11)	UMIC	11/9009	71/8858	0.152 (0.081, 0.287)		
Salinas B (2005)	Brazil, Mexico, Venezuela	UMIC	5/464	34/454	0.144 (0.057, 0.365)		
Tregnaghi MW (2011)	Latin America (6)	UMIC	7/4211	19/2099	0.184 (0.077, 0.436)		
Madhi SA (2010)	South Africa	UMIC	9/971	32/960	0.278 (0.133, 0.579)		
Colgate ER (2016)	Bangladesh	LMIC	9/292	35/301	0.265 (0.130, 0.542)		
Subtotal-MIC					0.205 (0.150, 0.278)	<0.001	0.0%
Madhi SA (2010)	Malawi	LIC	21/525	38/483	0.508 (0.303, 0.854)		
Subtotal-LIC					0.508 (0.303, 0.854)	0.011	\
Total					0.186 (0.117, 0.298)	<0.001	65.9%
Second year follow-up							
Vesikari T (2007)	Europe (6)	HIC	19/2554	67/1294	0.144 (0.087, 0.238)		
Phua KB (2012)	Singapore, Hong Kong, Taiwan	HIC	2/5221	36/5194	0.055 (0.013, 0.229)		
Subtotal-HIC					0.111 (0.047, 0.264)	<0.001	40.1%
Li RC (2014)	China	UMIC	13/1500	43/1479	0.298 (0.161, 0.552)		
Linhares AC (2008)	Latin America (10)	UMIC	22/7175	103/7062	0.210 (0.133, 0.333)		
Subtotal-MIC					0.238 (0.165, 0.344)	<0.001	0.0%
Cunliffe NA (2011)	Malawi	LIC	18/413	17/380	0.974 (0.510, 1.863)		
Subtotal-LIC					0.974 (0.510, 1.863)	0.937	\
Total					0.241 (0.115, 0.504)	<0.001	85.2%
Two years follow-up							
Vesikari T (2007)	Europe (6)	HIC	24/2572	127/1302	0.096 (0.062, 0.147)		
Phua KB (2009)	Singapore, Hong Kong, Taiwan	HIC	2/5263	51/5256	0.039 (0.010, 0.161)		
Kawamura N (2011)	Japan	HIC	2/498	12/250	0.084 (0.019, 0.371)		
Subtotal-HIC					0.088 (0.059, 0.131)	<0.001	0.0%
Linhares AC (2008)	Latin America (10)	UMIC	32/7205	161/7081	0.195 (0.134, 0.285)		
Li RC (2014)	China	UMIC	21/1575	75/1573	0.280 (0.173, 0.451)		
Subtotal-MIC					0.227 (0.160, 0.320)	<0.001	25.0%
Cunliffe NA (2011)	Malawi	LIC	38/525	53/483	0.660 (0.443, 0.982)		
Subtotal-LIC					0.660 (0.443, 0.982)	0.040	\
Total					0.174 (0.083, 0.364)	<0.001	90.6%
Three years follow-up							
Phua KB (2012)	Singapore, Hong Kong, Taiwan	HIC	2/5263	64/5256	0.031(0.008,0.127)	<0.001	\
RV5							
First year follow-up							
Goveia MG (2008)	The USA, Europe (5), Latin America (5)	HIC	1/2535	51/2563	0.020 (0.003, 0.143)		
Block SL (2007)	The USA, Finland	HIC	0/651	6/661	0.078 (0.004, 1.384)		
Iwata S (2013)	Japan	HIC	0/380	10/381	0.048 (0.003, 0.812)		
Subtotal-HIC					0.034 (0.008, 0.141)	<0.001	0.0%
Grant LR (2012)	American Indian tribes	UMIC	3/295	26/288	0.113 (0.034, 0.368)		
Mo ZJ (2017)	China	UMIC	11/1930	52/1946	0.213 (0.112, 0.408)		
Zaman K (2010)	Bangladesh, Vietnam	LMIC	19/991	38/978	0.493 (0.287, 0.850)		
Armah GE (2010)	Ghana, Kenya	LMIC	17/1556	54/1562	0.316 (0.184, 0.543)		
Subtotal-MIC					0.284 (0.170, 0.475)	<0.001	57.3%
Sow SO (2012)	Mali	LIC	4/845	4/843	0.998 (0.250, 3.976)		
Subtotal-LIC					0.998 (0.250, 3.976)	0.997	\
Total					0.251 (0.124, 0.506)	<0.001	69.1%
Second year follow-up							
Vesikari K (2009)	Europe (5)	HIC	1/667	18/694	0.058 (0.008, 0.432)		
Subtotal-HIC					0.058 (0.008, 0.432)	0.005	\
Zaman K (2010)	Bangladesh, Vietnam	LMIC	19/991	33/978	0.568 (0.325, 0.992)		
Armah GE (2010)	Ghana, Kenya	LMIC	14/1528	17/1522	0.820 (0.406, 1.658)		
Subtotal-MIC					0.655 (0.423, 1.013)	0.057	\
Sow SO (2012)	Mali	LIC	43/829	53/826	0.808 (0.547, 1.195)		
Subtotal-LIC					0.808 (0.547, 1.195)	0.286	\
Total					0.618 (0.360, 1.059)	0.080	60.5%
Two years follow-up							
Vesikari T (2006)	The USA, Europe (5), Latin America (5)	HIC	3/2207	68/2305	0.046 (0.015, 0.146)		
Subtotal-HIC					0.046 (0.015, 0.146)	<0.001	\
Zaman K (2010)	Bangladesh, Vietnam	LMIC	38/991	71/978	0.528 (0.360, 0.775)		
Armah GE (2010)	Ghana, Kenya	LMIC	31/1534	71/1523	0.433 (0.286, 0.657)		
Subtotal-MIC					0.482 (0.364, 0.639)	<0.001	0.0%

Sow SO (2012)	Mali	LIC	48/823	58/825	0.830 (0.573, 1.201)		
Subtotal-LIC					0.830 (0.573, 1.201)	0.322	\
Total					0.377 (0.186, 0.765)	0.007	88.6%
Rotavac							
First year follow-up							
Bhandari N (2014)	India	LMIC	56/4354	64/2187	0.440 (0.308, 0.627)	<0.001	\
Second year follow-up							
Bhandari N (2014)	India	LMIC	15/4354	12/2187	0.628 (0.294, 1.339)	0.228	\
Two years follow-up							
Bhandari N (2014)	India	LMIC	71/4354	76/2187	0.469 (0.341, 0.646)	<0.001	\
BRV-PV							
First year follow-up							
Isanaka S (2017)	Niger	LIC	31/1780	87/1728	0.346 (0.231, 0.518)		
Kulkarni PS (2017)	India	LMIC	61/3527	94/3498	0.644 (0.468, 0.885)		
Total					0.478 (0.260, 0.879)	0.017	82.1%
Second year follow-up							
Kulkarni PS (2017)	India	LMIC	110/3533	181/3502	0.602 (0.478, 0.760)	<0.001	\
Two years follow-up							
Kulkarni PS (2017)	India	LMIC	171/3533	275/3502	0.616 (0.512, 0.742)	<0.001	\
LLR							
First year follow-up							
Shengli X (2020)	China	UMIC	16/4582	65/4611	0.248 (0.144, 0.427)	<0.001	\
Second year follow-up							
Shengli X (2020)	China	UMIC	47/4359	153/4422	0.312 (0.225, 0.431)	<0.001	\
Two years follow-up							
Shengli X (2020)	China	UMIC	63/4359	215/4422	0.297 (0.225, 0.392)	<0.001	\

Table 7. Estimated Pooled Vaccine Protection against Severe RVGE Stratified by Income Development

Studies	Countries and regions	Income	Case (Vaccinated/N)	Control (Vaccinated/N)	OR (95% CI)	P	I ²
RV1							
2 doses							
Sammy K (2019)	Kenya	LMIC	17/30	102/125	0.295(0.126, 0.691)		
Umid E (2020)	Uzbekistan	LMIC	18/23	400/452	0.468(0.167,1.314)		
Cantilloa KC (2014)	Colombia	UMIC	110/117	670/711	0.962 (0.421, 2.198)		
Beres LK (2016)	Zambia	LMIC	23/34	182/270	1.011 (0.472, 2.167)		
Gastañaduy PA (2016)	Guatemala	LMIC	64/82	288/317	0.358 (0.187, 0.684)		
Patel MM (2013)	Bolivia, South America	LMIC	196/281	1313/1499	0.327(0.243, 0.440)		
Armah G (2016)	Ghana	LMIC	12/13	426/439	0.366 (0.044, 3.031)		
Pringle KD (2016)	Bolivia	LMIC	181/263	250/303	0.468 (0.315, 0.695)		
Lopez AL (2018)	Philippines	LMIC	23/35	177/202	0.271 (0.120, 0.611)		
Palma O (2010)	El Salvador	LMIC	121/174	468/556	0.429 (0.289, 0.637)		
Subtotal-MIC					0.431 (0.338, 0.551)	<0.001	36.1%
Zeev NB (2015)	Malawi	LIC	69/82	434/463	0.355 (0.176, 0.715)		
Subtotal-LIC					0.355 (0.176, 0.715)	0.004	\
Total					0.396 (0.329, 0.478)	<0.001	9.1%
1 dose							
Beres LK (2016)	Zambia	LMIC	1/12	28/116	0.286 (0.035, 2.312)		
Gastañaduy PA (2016)	Guatemala	LMIC	14/32	51/80	0.442 (0.192, 1.018)		
Patel MM (2013)	Bolivia, South America	LMIC	92/177	338/524	0.596 (0.422, 0.841)		
Armah G (2016)	Ghana	LMIC	0/1	11/24	0.391 (0.014, 10.565)		
Pringle KD (2016)	Bolivia	LMIC	55/137	41/94	0.867 (0.509, 1.476)		
Lopez AL (2018)	Philippines	LMIC	4/16	19/44	0.439 (0.122, 1.576)		
Palma O (2010)	El Salvador	LMIC	49/102	113/201	0.720 (0.446, 1.161)		
Subtotal-MIC					0.640 (0.508, 0.806)	<0.001	0.0%
Zeev NB (2015)	Malawi	LIC	11/24	43/72	0.571 (0.225, 1.448)		
Subtotal-LIC					0.571 (0.225, 1.448)	0.238	\
Total					0.636 (0.508, 0.795)	<0.001	0.0%
RV5							
3 doses							
Patel M (2009)	Nicaragua	LMIC	110/146	616/717	0.501 (0.326, 0.771)		
Mast TC (2011)	Nicaragua	LMIC	241/300	1523/1643	0.322 (0.229, 0.452)		
Subtotal-MIC					0.393 (0.255, 0.606)	<0.001	60.6%
Bonkougou IJO (2017)	Burkina Faso	LIC	101/131	331/391	0.610 (0.373, 0.998)		
Subtotal-LIC					0.610 (0.373, 0.998)	0.049	\
Total					0.448 (0.303, 0.661)	<0.001	61.8%
2 doses							
Bonkougou IJO (2017)	Burkina Faso	LIC	14/44	41/101	0.683 (0.323, 1.443)	0.318	\
1 dose							
Bonkougou IJO (2017)	Burkina Faso	LIC	8/38	22/82	0.727 (0.290, 1.825)	0.498	\

Table 8. Estimated Pooled Vaccine Protection against Severe AGE Stratified by Income Development at Different Follow-up Times

Studies	Countries or regions	Income	Vaccine(n/N)	Placebo(n/N)	RR (95% CI)	P	I ²
RV1							
First year follow-up							
Phua KB (2012)	Singapore, Hong Kong, Taiwan	HIC	54/5263	80/5256	0.674 (0.478, 0.950)		
Phua KB (2005)	Singapore	HIC	5/639	10/642	0.502 (0.173, 1.461)		
Vesikari T (2007)	Europe (6)	HIC	116/2572	123/1302	0.477 (0.374, 0.610)		
Subtotal-HIC					0.545 (0.425, 0.698)	<0.001	23.0%
Tregnaghi MW (2011)	Latin America (6)	UMIC	116/4211	78/2099	0.741 (0.559, 0.983)		
Ruiz-Palacios GM (2006)	Latin America (11), Finland	UMIC	183/9009	300/8858	0.600 (0.500, 0.719)		
Madhi SA (2010)	South Africa	UMIC	69/1944	61/960	0.559 (0.399, 0.781)		
Rojas OL (2007)	Colombia	UMIC	0/159	6/160	0.077 (0.004, 1.363)		
Colgate ER (2016)	Bangladesh	LMIC	65/292	86/301	0.779 (0.589, 1.03)		
Subtotal-MIC					0.655 (0.552, 0.777)	<0.001	35.1%
Madhi SA (2010)	Malawi	LIC	187/1030	117/483	0.749 (0.611, 0.919)		
Subtotal-LIC					0.749 (0.611, 0.919)	0.006	\
Total					0.641 (0.558, 0.737)	<0.001	42.8%
Second year follow-up							
Phua KB (2012)	Singapore, Hong Kong, Taiwan	HIC	87/5221	131/5194	0.661 (0.505, 0.864)		
Vesikari T (2007)	Europe (6)	HIC	149/2554	153/1294	0.493 (0.398, 0.612)		
Subtotal-HIC					0.565 (0.424, 0.751)	<0.001	64.0%
Cunliffe NA (2011)	Malawi	LIC	67/413	71/380	0.868 (0.641, 1.176)		
Subtotal-LIC					0.868 (0.641, 1.176)	0.361	\
Total					0.648 (0.468, 0.895)	0.009	78.4%
Two years follow-up							
Phua KB (2009)	Singapore, Hong Kong, Taiwan	HIC	141/5263	202/5256	0.697 (0.564, 0.861)		
Vesikari T (2007)	Europe (6)	HIC	256/2572	257/1302	0.504 (0.430, 0.592)		
Subtotal-HIC					0.588 (0.428, 0.809)	0.001	82.7%
Li RC (2014)	China	UMIC	187/1575	206/1573	0.907 (0.753, 1.091)		
Linhares AC (2008)	Latin America (10)	UMIC	342/7205	551/7081	0.610 (0.535, 0.695)		
Subtotal-MIC					0.739 (0.501, 1.091)	0.128	91.5%
Cunliffe NA (2011)	Malawi	LIC	146/525	160/483	0.840 (0.696, 1.012)		
Subtotal-LIC					0.840 (0.696, 1.012)	0.067	\
Total					0.693 (0.561, 0.854)	0.001	86.7%
RV5							
First year follow-up							
Breiman RF (2012)	Bangladesh, Vietnam	LMIC	46/991	62/978	0.732 (0.505, 1.061)		
Tapia MD (2012)	Ghana, Kenya	LMIC	70/1234	100/1214	0.689 (0.513, 0.915)		
Subtotal-MIC					0.705 (0.560, 0.888)	0.003	0.0%
Tapia MD (2012)	Mali	LIC	55/823	56/814	0.971 (0.678, 1.391)		
Subtotal-LIC					0.971 (0.678, 1.391)	0.874	\
Total					0.776 (0.632, 0.953)	0.016	10.1%
Second year follow-up							
Breiman RF (2012)	Bangladesh, Vietnam	LMIC	26/991	34/978	0.755 (0.456, 1.248)		
Tapia MD (2012)	Ghana, Kenya	LMIC	25/817	22/794	1.104 (0.628, 1.942)		
Subtotal-MIC					0.893 (0.614, 1.300)	0.555	0.0%
Tapia MD (2012)	Mali	LIC	48/444	53/451	0.920 (0.637, 1.329)		
Subtotal-LIC					0.920 (0.637, 1.329)	0.657	\
Total					0.907 (0.697, 1.179)	0.465	0.0%
Two years follow-up							
Zaman K (2010)	Bangladesh, Vietnam	LMIC	81/991	107/978	0.747 (0.568, 0.983)		
Tapia MD (2012)	Ghana, Kenya	LMIC	105/1219	130/1197	0.793 (0.621, 1.013)		
Subtotal-MIC					0.772 (0.643, 0.927)	0.006	0.0%
Tapia MD (2012)	Mali	LIC	147/797	148/795	0.991 (0.806, 1.217)		
Subtotal-LIC					0.991 (0.806, 1.217)	0.930	\
Total					0.852 (0.714, 1.016)	0.075	38.5%
Rotavac							
First year follow-up							
Bhandari N (2014)	India	LMIC	221/4354	145/2187	0.766 (0.625, 0.938)	0.010	\
Second year follow-up							
Bhandari N (2014)	India	LMIC	87/4354	43/2187	1.016 (0.708, 1.459)	0.930	\
Two years follow-up							
Bhandari N (2014)	India	LMIC	308/4354	188/2187	0.823 (0.692, 0.979)	0.028	\
BRV-PV							
First year follow-up							
Kulkarni PS (2017)	India	LMIC	364/3527	379/3498	0.953 (0.831, 1.091)		
Isanaka S (2017)	Niger	LIC	214/1780	229/1728	0.907 (0.762, 1.080)		
Total					0.935 (0.840, 1.041)	0.220	0.0%
Second year follow-up							
Kulkarni PS (2017)	India	LMIC	440/3533	453/3502	0.963 (0.852, 1.088)	0.544	\
Two years follow-up							
Kulkarni PS (2017)	India	LMIC	804/3533	832/3502	0.958 (0.880, 1.043)	0.320	\

Table 9. Estimated Pooled Vaccine Protection against RVGE Stratified by Income Development at Different Follow-up Times

Studies	Countries and regions	Income	Vaccine(n/N)	Placebo(n/N)	RR (95% CI)	P	I ²
RV1							
First year follow-up							
Bernstein DI (1999)	The USA	HIC	2/108	18/107	0.110 (0.026, 0.463)		
Vesikari T (2007)	Europe (6)	HIC	24/2572	94/1302	0.129 (0.083, 0.201)		
Subtotal-HIC					0.127 (0.083, 0.195)	<0.001	0.0%
Li RC (2014)	China	UMIC	27/1575	90/1573	0.300 (0.196, 0.458)		
Ruiz-Palacios GM (2007)	Mexico	UMIC	3/78	12/87	0.279 (0.082, 0.952)		
Salinas B (2005)	Brazil, Mexico, Venezuela	UMIC	15/464	49/454	0.300 (0.170, 0.526)		
Justino MC (2012)	Brazil	UMIC	2/309	5/300	0.388 (0.076, 1.986)		
Madhi SA (2010)	South Africa	UMIC	82/1944	113/960	0.358 (0.273, 0.471)		
Rojas OL (2007)	Colombia	UMIC	5/159	20/160	0.252 (0.097, 0.654)		
Colgate ER (2016)	Bangladesh	LMIC	49/292	103/301	0.490 (0.363, 0.662)		
Zaman K (2009)	Bangladesh	LMIC	3/196	4/98	0.375 (0.086, 1.643)		
Subtotal-MIC					0.373 (0.316, 0.441)	<0.001	0.0%
Madhi SA (2010)	Malawi	LIC	85/1030	61/483	0.653 (0.479, 0.891)		
Subtotal-LIC					0.653 (0.479, 0.891)	0.007	\
Total					0.316 (0.224, 0.448)	<0.001	77.2%
Second year follow-up							
Vesikari T (2007)	Europe (6)	HIC	61/2554	110/1294	0.281 (0.207, 0.381)		
Subtotal-HIC					0.281 (0.207, 0.381)	<0.001	\
Li RC (2014)	China	UMIC	43/1500	78/1479	0.544 (0.377, 0.783)		
Justino MC (2012)	Brazil	UMIC	7/309	23/300	0.295 (0.129, 0.678)		
Subtotal					0.451 (0.260, 0.783)	0.005	42.4%
Cunliffe NA (2011)	Malawi	LIC	28/413	20/380	1.288 (0.738, 2.248)		
Subtotal-LIC					1.288 (0.738, 2.248)	0.420	\
Total					0.494 (0.255, 0.955)	0.036	87.9%
Two years follow-up							
Kawamura N (2011)	Japan	HIC	14/498	34/250	0.207 (0.113, 0.378)		
Vesikari T (2007)	Europe (6)	HIC	85/2572	204/1302	0.211 (0.165, 0.269)		
Subtotal-HIC					0.210 (0.168, 0.264)	<0.001	0.0%
Justino MC (2012)	Brazil	UMIC	9/309	28/300	0.312 (0.150, 0.650)		
Li RC (2014)	China	UMIC	70/1575	167/1573	0.419 (0.320, 0.548)		
Subtotal-MIC					0.404 (0.314, 0.521)	<0.001	0.0%
Cunliffe NA (2011)	Malawi	LIC	73/525	83/483	0.809 (0.606, 1.081)		
Subtotal-LIC					0.809 (0.606, 1.081)	0.151	\
Total					0.348 (0.196, 0.618)	<0.001	92.5%
RV5							
First year follow-up							
Vesikari T (2006)	The USA, Europe (5), Latin America(5)	HIC	82/2207	315/2305	0.272 (0.215, 0.344)		
Block SL (2007)	The USA, Finland	HIC	15/651	54/661	0.282 (0.161, 0.495)		
Vesikari T (2006)	Finland	HIC	12/237	43/264	0.311 (0.168, 0.575)		
Iwata S (2013)	Japan	HIC	7/380	28/381	0.251 (0.111, 0.567)		
Subtotal-HIC					0.276 (0.226, 0.336)	<0.001	0.0%
Grant LR (2012)	American Indian tribes	UMIC	16/295	63/288	0.248 (0.147, 0.419)		
Mo ZJ (2017)	China	UMIC	34/1930	109/1946	0.315 (0.215, 0.460)		
Breiman RF (2012)	Bangladesh, Vietnam	LMIC	29/991	63/978	0.454 (0.295, 0.699)		
Tapia MD (2012)	Ghana, Kenya	LMIC	37/1556	91/1562	0.408 (0.280, 0.594)		
Subtotal-MIC					0.356 (0.279, 0.453)	<0.001	24.7%
Tapia MD (2012)	Mali	LIC	22/845	24/843	0.914 (0.517, 1.618)		
Subtotal-LIC					0.914 (0.517, 1.618)	0.759	\
Total					0.364 (0.281, 0.473)	<0.001	63.0%
Second year follow-up							
Vesikari K (2009)	Europe (5)	HIC	44/649	95/601	0.497 (0.353, 0.699)		
Subtotal-HIC					0.497 (0.353, 0.699)	<0.001	\
Breiman RF (2012)	Bangladesh, Vietnam	LMIC	36/991	47/978	0.756 (0.494, 1.156)		
Tapia MD (2012)	Ghana, Kenya	LMIC	18/1242	21/1216	0.839 (0.449, 1.567)		
Subtotal-MIC					0.781 (0.550, 1.110)	0.169	0.0%
Tapia MD (2012)	Mali	LIC	129/838	158/836	0.815 (0.659, 1.007)		
Subtotal-LIC					0.815 (0.659, 1.007)	0.058	\
Total					0.703 (0.541, 0.913)	0.008	51.2%
Two years follow-up							
Vesikari T (2006)	The USA, Europe (5), Latin America(5)	HIC	118/2207	403/2305	0.306 (0.251, 0.372)		
Subtotal-HIC					0.306 (0.251, 0.372)	<0.001	\
Zaman K (2010)	Bangladesh, Vietnam	LMIC	65/991	109/978	0.589 (0.439, 0.790)		
Tapia MD (2012)	Ghana, Kenya	LMIC	55/1551	112/1557	0.493 (0.360, 0.675)		
Subtotal-MIC					0.542 (0.437, 0.672)	<0.001	0.0%
Tapia MD (2012)	Mali	LIC	151/832	182/835	0.833 (0.686, 1.010)		
Subtotal-LIC					0.833 (0.686, 1.010)	0.063	\
Total					0.521 (0.316, 0.861)	0.011	94.3%
Rotavac							

First year follow-up							
Bhandari N (2014)	India	LMIC	226/4354	171/2187	0.664(0.548,0.804)	<0.001	\
Second year follow-up							
Bhandari N(2014)	India	LMIC	51/4354	30/2187	0.854 (0.546, 1.337)	0.490	\
Two years follow-up							
Bhandari N(2014)	India	LMIC	277/4354	201/2187	0.692 (0.582, 0.824)	<0.001	\
<hr/>							
BRV-PV							
First year follow-up							
Kulkarni PS (2017)	India	LMIC	144/3527	197/3498	0.725 (0.588, 0.894)		
Isanaka S (2017)	Niger	LIC	121/1780	172/1728	0.683 (0.546, 0.853)		
Subtotal					0.705 (0.605, 0.821)	<0.001	0.0%
Second year follow-up							
Kulkarni PS (2017)	India	LMIC	348/3533	417/3502	0.827 (0.723, 0.946)	0.006	\
Two years follow-up							
Kulkarni PS (2017)	India	LMIC	492/3533	614/3502	0.794 (0.712, 0.886)	<0.001	\
<hr/>							
LLR							
First year follow-up							
Shengli X (2020)	China	UMIC	125/4582	309/4611	0.407 (0.332, 0.499)	<0.001	\
Second year follow-up							
Shengli X (2020)	China	UMIC	216/4359	488/4422	0.449 (0.385, 0.524)	<0.001	\
Two years follow-up							
Shengli X (2020)	China	UMIC	337/4359	788/4422	0.434 (0.385, 0.489)	<0.001	\

eTable 10. Estimated Pooled Vaccine Protection against RVGE Hospitalization and ED visits Stratified by Income Development at Different Follow-up Times

Studies	Countries and regions	Income	Vaccine(n/N)	Placebo(n/N)	RR (95% CI)	P	I ²
RV1							
First year follow-up							
Bernstein DI (1999)	The USA	HIC	0/108	2/107	0.198 (0.010, 4.080)		
Phua KB (2012)	Singapore, Hong Kong, Taiwan	HIC	0/5263	13/5256	0.037 (0.002, 0.622)		
Vesikari T (2007)	Europe (6)	HIC	0/2572	12/1302	0.020 (0.001, 0.342)		
Subtotal-HIC					0.050 (0.009, 0.264)	<0.001	0.0%
Li RC (2014)	China	UMIC	2/1575	14/1573	0.143 (0.032, 0.627)		
Tregnaghi MW (2011)	Latin America (6)	UMIC	4/4211	17/2099	0.117 (0.040, 0.348)		
Ruiz-Palacios GM (2006)	Latin America (11), Finland	UMIC	9/9009	59/8858	0.150 (0.074, 0.302)		
Madhi SA (2010)	South Africa, Malawi	LMIC	14/2974	16/1443	0.425 (0.208, 0.867)		
Subtotal-MIC					0.197 (0.101, 0.382)	<0.001	51.1%
Total					0.161 (0.083, 0.313)	<0.001	43.6%
Second year follow-up							
Vesikari T (2007)	Europe (6)	HIC	2/2554	13/1294	0.078 (0.018, 0.345)		
Phua KB (2012)	Singapore, Hong Kong, Taiwan	HIC	1/5221	35/5194	0.028 (0.004, 0.207)		
Subtotal-HIC					0.054 (0.016, 0.179)	<0.001	0.0%
Li RC (2014)	China	UMIC	2/1500	7/1479	0.282 (0.059, 1.354)	0.114	\
Subtotal-MIC					0.282 (0.059, 1.354)		
Total					0.093 (0.025, 0.347)	<0.001	46.2%
Two years follow-up							
Vesikari T (2006)	Europe (6)	HIC	2/2572	25/1302	0.040 (0.010, 0.171)		
Laua YL (2013)	Hong Kong	HIC	2/1494	23/1499	0.087 (0.021, 0.369)		
Kawamura N (2011)	Japan	HIC	1/498	2/250	0.251 (0.023, 2.755)		
Subtotal-HIC					0.074 (0.029, 0.189)	<0.001	0.0%
Li RC (2014)	China	UMIC	4/1575	21/1573	0.190 (0.065, 0.553)		
Linhares AC (2008)	Latin America (10)	UMIC	22/7205	127/7081	0.170 (0.108, 0.267)		
Subtotal-MIC					0.173 (0.114, 0.262)	<0.001	0.0%
Total					0.144 (0.091, 0.228)	<0.001	10.2%
RV5							
First year follow-up							
Grant LR (2012)	America Indian tries	UMIC	0/295	3/288	0.139 (0.007, 2.688)		
Christie C (2012)	Jamaica	UMIC	0/752	8/746	0.058 (0.003, 1.009)		
Subtotal-MIC					0.089 (0.011, 0.691)	0.021	0.0%
Two years follow-up							
Vesikari T (2007)	Europe (5)	HIC	16/14018	301/13984	0.053 (0.032, 0.088)		
Vesikari T (2007)	The USA	HIC	3/12284	58/12179	0.051 (0.016, 0.164)		
Subtotal-HIC					0.053 (0.033, 0.084)	<0.001	0.0%
Vesikari T (2007)	Latin America (5)	UMIC	1/2252	10/2237	0.099 (0.013, 0.775)		
Subtotal-MIC					0.099 (0.013, 0.775)	0.028	\
Total					0.054 (0.034, 0.085)	<0.001	0.0%
Rotavac							
First year follow-up							
Bhandari N (2014)	India	LMIC	218/4354	161/2187	0.680 (0.558,0.828)	<0.001	\
Second year follow-up							
Bhandari N (2014)	India	LMIC	59/4354	40/2187	0.741 (0.498, 1.103)	0.140	\
Two years follow-up							
Bhandari N (2014)	India	LMIC	277/4364	201/2187	0.692 (0.582, 0.824)	<0.001	\
BRV-PV							
First year follow-up							
Kulkarni PS (2017)	India	LMIC	35/3527	53/3498	0.655 (0.428, 1.001)	0.051	\
Second year follow-up							
Kulkarni PS (2017)	India	LMIC	60/3527	87/3502	0.685 (0.494, 0.948)	0.023	\
Two years follow-up							
Kulkarni PS (2017)	India	LMIC	95/35a7	140/3502	0.673 (0.521, 0.869)	0.002	\
LLR							
First year follow-up							
Shengli X (2020)	China	UMIC	9/4582	31/4611	0.292 (0.139, 0.613)	0.001	\
Second year follow-up							
Shengli X (2020)	China	UMIC	11/4359	48/4422	0.232 (0.121, 0.447)	<0.001	\
Two years follow-up							
Shengli X (2020)	China	UMIC	20/4359	78/4422	0.260 (0.159, 0.424)	<0.001	\

Table 11. Estimated Pooled Vaccine Protection against RVGE Stratified by Income Development

Studies	Countries and regions	Income	Case (Vaccinated/N)	Control (Vaccinated/N)	OR (95% CI)	P	I ²
RV1							
2 doses							
Julia EM (2020)	Australia	HIC	1977/2747	24902/27465	0.264(0.241,0.290)		
Araki K (2018)	Japan	HIC	36/456	226/724	0.189 (0.130, 0.275)		
Castilla J (2012)	Navarre, Spain	HIC	19/730	459/5401	0.288 (0.181, 0.458)		
Araki K (2018)	Saga City, Japan	HIC	3/64	162/720	0.169 (0.052, 0.547)		
Subtotal-HIC					0.251 (0.213, 0.295)	<0.001	18.2%
Jemma L (2019)	Kenya	LMIC	1126/1516	653/826	0.765(0.624,0.937)		
Beres LK (2016)	Zambia	LMIC	52/84	182/270	0.786 (0.472, 1.307)		
Subtotal-MIC					0.768(0.636,0.927)	0.006	0.0%
Total					0.354(0.204,0.613)	<0.001	95.4%
1 dose							
Castilla J (2012)	Navarre, Spain	HIC	2/713	77/2019	0.181 (0.044, 0.737)		\
Julia EM (2020)	Australia	HIC	184/954	1808/4371	0.339(0.285,0.402)		
Subtotal-HIC					0.336(0.283,0.398)	<0.001	0.0%
Beres LK (2016)	Zambia	LMIC	7/39	28/116	0.688 (0.273, 1.728)		\
Jemma L (2019)	Kenya	LMIC	186/576	130/303	0.635(0.476,0.845)		
Subtotal-MIC					0.639(0.486,0.841)	0.001	0.0%
Total					0.449(0.271,0.744)	0.002	81.5%
RV5							
3 doses							
Araki K (2018)	Japan	HIC	27/447	179/677	0.179 (0.117, 0.274)		
Castilla J (2012)	Navarre, Spain	HIC	15/726	390/5332	0.267 (0.159, 0.450)		
Araki K (2018)	Saga City, Japan	HIC	0/61	91/649	0.050 (0.003, 0.809)		
Subtotal-HIC					0.207 (0.140, 0.304)	<0.001	16.2%
Tate JE(2016)	Rwanda	LIC	5/38	49/130	0.250 (0.092, 0.684)		
Subtotal-LIC					0.250 (0.092, 0.684)	0.007	\
Total					0.210 (0.154, 0.286)	<0.001	0.0%
2 doses							
Tate JE (2016)	Rwanda	LIC	7/40	7/88	2.455 (0.798,7.546)		
Total					2.455 (0.798,7.546)	0.117	\
1 or 2 doses							
Tate JE (2016)	Rwanda	HIC	7/40	7/88	2.455 (0.798,7.546)		
Castilla J (2012)	Navarre, Spain	HIC	9/720	168/5110	0.371 (0.190, 0.731)		
Total					0.905 (0.140, 5.854)	0.917	87.7%
LLR							
2 doses							
Fu C (2012)	Guangzhou, China	UMIC	9/2747	19/3020	0.519 (0.235, 1.149)	0.106	\
1 dose							
Fu C (2012)	Guangzhou, China	UMIC	383/3121	587/3588	0.715 (0.622, 0.822)	<0.001	\
≥ 1 dose							
Fu C (2012)	Guangzhou, China	UMIC	392/3130	606/3607	0.709 (0.618, 0.813)		
Zhen SS (2015)	Hebei, China	UMIC	51/305	304/1220	0.605 (0.436, 0.839)		
Li J (2019)	Beijing, China	UMIC	60/255	196/256	0.094 (0.063, 0.142)		
Subtotal					0.348 (0.121, 0.999)	0.050	97.6%

Table 12. Estimated Pooled Vaccine Protection Against RVGE Hospitalization Stratified by Income Development

Studies	Countries and regions	Income	Case (Vaccinated/N)	Control (Vaccinated/N)	OR (95% CI)	P	I ²
RV1							
2 doses							
Immergluck LC (2016)	the USA	HIC	16/51	48/69	0.200 (0.091, 0.438)		
Margaret M (2013)	the USA	HIC	22/95	745/1442	0.282 (0.173, 0.459)		
Dolla MK (2015)	Quebec	HIC	7/31	254/316	0.071 (0.029, 0.173)		
Braeckman T (2012)	Belgium	HIC	66/145	165/182	0.086 (0.047, 0.156)		
Chang WC (2013)	Taiwan, China	HIC	3/184	275/1623	0.081 (0.026, 0.256)		
Subtotal-HIC					0.131 (0.071, 0.242)	<0.001	70.3%
Groome MJ (2014)	South Africa	UMIC	278/414	856/1100	0.583 (0.454, 0.748)		
Ichihara MYT (2014)	Brazil	UMIC	115/182	1481/1682	0.233 (0.167, 0.326)		
Justino MCA (2011)	Brazil	UMIC	289/436	564/690	0.439 (0.333, 0.579)		
Cantilloa KC (2014)	Colombia	UMIC	143/156	670/711	0.673 (0.352, 1.289)		
Mokomane M (2017)	Botswana	UMIC	162/205	288/317	0.379 (0.228, 0.631)		
Snelling TL (2009)	Indigenous Australia	UMIC	3/14	32/57	0.213 (0.054, 0.847)		
Beres LK (2016)	Zambia	LMIC	8/17	182/270	0.430 (0.160, 1.152)		
Gastañaduy PA (2016)	Guatemala	LMIC	41/125	265/483	0.402 (0.265, 0.608)		
Gastañaduy PA (2016)	Guatemala	LMIC	162/205	288/317	0.379 (0.228, 0.631)		
Patel MM (2013)	Bolivia, South America	LMIC	208/300	1367/1561	0.321 (0.241, 0.428)		
Pringle KD (2016)	Bolivia	LMIC	203/294	298/362	0.479 (0.332, 0.691)		
Armah G (2016)	Ghana	LMIC	196/206	426/439	0.598 (0.258, 1.388)		
Gheorghita S (2016)	Moldova	LMIC	14/89	348/745	0.213 (0.118, 0.384)		
Lopez AL (2018)	Philippines	LMIC	78/107	177/202	0.380 (0.209, 0.691)		
Palma O (2010)	El Salvador	LMIC	152/251	617/770	0.381 (0.280, 0.519)		
Sammy K (2019)	Kenya	LMIC	51/84	308/377	0.346(0.208,0.576)		
Umid E (2020)	Uzbekistan	LMIC	76/92	400/452	0.618(0.335,1.138)		
Subtotal-MIC					0.396(0.338,0.465)	<0.001	52.1%
Zeev NB (2015)	Malawi	LIC	81/97	520/565	0.438 (0.236, 0.812)		
Mujuru HA (2018)	Zimbabwe	LIC	853/888	2527/2640	1.090 (0.740, 1.605)		
Subtotal-LIC					0.714 (0.292, 1.745)	0.460	83.5%
Total					0.432(0.343,0.544)	<0.001	66.4%
1 dose							
Chang WC (2013)	Taiwan, China	HIC	0/181	10/1358	0.354 (0.021, 6.063)		
Dolla MK (2015)	Quebec	HIC	1/25	26/88	0.099 (0.013, 0.773)		
Immergluck LC (2016)	the USA	HIC	3/38	4/25	0.450 (0.092, 2.210)		
Subtotal-HIC					0.269 (0.085, 0.850)	0.025	0.0%
Snelling TL (2009)	Indigenous Australia	UMIC	7/18	26/51	0.612 (0.205, 1.829)		
Groome MJ (2014)	South Africa	UMIC	126/262	334/578	0.677 (0.505, 0.907)		
Ichihara MYT (2014)	Brazil	UMIC	33/100	279/480	0.355 (0.225, 0.559)		
Justino MCA (2011)	Brazil	UMIC	77/224	118/244	0.559 (0.395, 0.812)		
Mokomane M (2017)	Botswana	UMIC	37/80	51/80	0.489 (0.260, 0.922)		
Beres LK (2016)	Zambia	LMIC	1/10	28/116	0.349 (0.042, 2.878)		
Gastañaduy PA (2016)	Guatemala	LMIC	37/80	51/80	0.489 (0.260, 0.922)		
Patel MM (2013)	Bolivia, South America	LMIC	100/192	357/551	0.591 (0.423, 0.824)		
Pringle KD (2016)	Bolivia	LMIC	60/151	57/121	0.740 (0.457, 1.200)		
Armah G (2016)	Ghana	LMIC	1/11	11/24	0.118 (0.013, 1.074)		
Gheorghita S (2016)	Moldova	LMIC	4/79	51/448	0.415 (0.146, 1.183)		
Lopez AL (2018)	Philippines	LMIC	11/40	19/44	0.499 (0.200, 1.246)		
Palma O (2010)	El Salvador	LMIC	72/171	199/352	0.559 (0.386, 0.809)		
Sammy K (2019)	Kenya	LMIC	7/40	41/110	0.357(0.145,0.880)		
Umid E (2020)	Uzbekistan	LMIC	10/26	47/99	0.691(0.286,1.672)		
Subtotal-MIC					0.559(0.489,0.640)	<0.001	0.0%
Zeev NB (2015)	Malawi	LIC	9/25	72/117	0.352 (0.143, 0.863)		
Mujuru HA (2018)	Zimbabwe	LIC	15/50	45/158	1.076 (0.536, 2.160)		
Subtotal-LIC					0.638 (0.214, 1.907)	0.422	73.2%
Total					0.578(0.483,0.690)	<0.001	0.0%
RV5							
3 doses							
Tate JE (2013)	the USA	HIC	22/127	351/700	0.208 (0.129, 0.338)		
Donauera S (2013)	the USA	HIC	2/68	371/927	0.045 (0.011, 0.187)		
Margaret M (2013)	the USA	HIC	6/79	287/748	0.132 (0.057, 0.307)		
Boom JA (2010)	the USA	HIC	5/72	76/214	0.136 (0.052, 0.351)		
Cortese MM (2011)	the USA	HIC	23/283	991/2861	0.167 (0.108, 0.257)		
Immergluck LC (2016)	the USA	HIC	22/57	34/55	0.388 (0.181, 0.832)		
Staat MA (2011)	the USA	HIC	17/167	282/745	0.186 (0.110, 0.314)		
Muhsen K (2018)	Israel	HIC	46/72	363/425	0.302 (0.174, 0.524)		
Chang WC (2013)	Taiwan, China	HIC	0/184	172/1520	0.021 (0.001, 0.342)		
Subtotal-HIC					0.186 (0.133, 0.260)	<0.001	56.9%
Patel M (2009)	Nicaragua	LMIC	158/209	868/1044	0.628 (0.441, 0.896)		
Mast TC (2011)	Nicaragua	LMIC	293/357	1444/1550	0.336 (0.240, 0.470)		
Patel M (2012)	Nicaragua	LMIC	773/849	7011/7309	0.432 (0.332, 0.562)		
Gastañaduy PA (2016)	Guatemala	LMIC	19/103	105/323	0.470 (0.271, 0.814)		

Subtotal-MIC						0.450 (0.347, 0.584)	<0.001	53.4%
Tate JE (2016)	Rwanda	LIC	3/29	36/90	0.173 (0.049, 0.615)			
Bonkougou IJO (2017)	Burkina Faso	LIC	133/172	488/582	0.657 (0.432, 0.999)			
Subtotal-LIC						0.386 (0.106, 1.410)	0.150	74.5%
Total						0.272 (0.197, 0.376)	<0.001	80.8%
2 doses								
Tate JE (2013)	the USA	HIC	8/113	146/495	0.182 (0.087, 0.383)			
Margaret M (2013)	the USA	HIC	2/75	9/48	0.119 (0.024, 0.577)			
Donauera S (2013)	the USA	HIC	3/69	144/700	0.176 (0.054, 0.566)			
Boom JA (2010)	the USA	HIC	2/69	41/179	0.100 (0.024, 0.428)			
Cortese MM (2011)	the USA	HIC	7/160	328/2115	0.249 (0.116, 0.537)			
Immergluck LC (2016)	the USA	HIC	3/38	8/29	0.225 (0.054, 0.943)			
Staat MA (2011)	the USA	HIC	7/157	140/603	0.154 (0.071, 0.337)			
Subtotal-HIC						0.179 (0.124, 0.260)	<0.001	0.0%
Patel M (2009)	Nicaragua	LIMC	42/93	257/433	0.564 (0.359, 0.886)			
Subtotal-MIC						0.564 (0.359, 0.886)	0.013	\
Bonkougou IJO (2017)	Burkina Faso	LIC	22/61	56/150	0.947 (0.510, 1.758)			
Subtotal-LIC						0.947 (0.510, 1.758)	0.863	\
Total						0.260 (0.149, 0.453)	<0.001	73.3%
1 dose								
Tate JE (2013)	the USA	HIC	9/114	110/459	0.272 (0.133, 0.555)			
Donauera S (2013)	the USA	HIC	5/71	139/695	0.303 (0.120, 0.766)			
Boom JA (2010)	the USA	HIC	5/72	59/197	0.175 (0.067, 0.455)			
Cortese MM (2011)	the USA	HIC	10/163	20/137	0.382 (0.172, 0.848)			
Immergluck LC (2016)	the USA	HIC	2/37	2/23	0.600 (0.079, 4.583)			
Staat MA (2011)	the USA	HIC	10/160	119/582	0.259 (0.133, 0.507)			
Subtotal-HIC						0.281 (0.198, 0.398)	<0.001	0.0%
Patel M (2009)	Nicaragua	LIMC	34/85	227/403	0.517 (0.321, 0.832)			
Subtotal-MIC						0.517 (0.321, 0.832)	0.007	\
Bonkougou IJO (2017)	Burkina Faso	LIC	9/48	29/123	0.748 (0.324, 1.726)			
Subtotal-LIC						0.748 (0.324, 1.726)	0.496	\
Total						0.365 (0.264, 0.504)	<0.001	25.3%
LLR								
2 doses								
Fua C (2007)	Guangzhou	UMIC	0/748	6/652	0.066 (0.004, 1.182)		0.065	\
1 dose								
Fua C (2007)	Guangzhou	UMIC	90/838	186/832	0.418 (0.318, 0.549)		<0.001	\

eTable 13. Indirect Comparisons between RV1 and RV5 Stratified by Income Development

Outcomes	No. of studies (RV1/RV5)	RR or OR (95% CI)	P-value
RCTs			
RVGE			
HIC	2/4	0.462 (0.290, 0.738)	0.001
MIC	8/4	1.048 (0.781, 1.407)	0.752
LIC	1/1	0.715 (0.373, 1.368)	0.311
Subtotal	10/7	0.865 (0.565, 1.325)	0.505
Severe RVGE			
HIC	3/3	2.067 (0.325, 13.139)	0.441
MIC	7/4	0.719 (0.397, 1.303)	0.277
LIC	1/1	0.510 (0.116, 2.231)	0.371
Subtotal	10/6	0.768 (0.335, 1.758)	0.532
RVGE			
Hospitalization			
MIC	4/2	2.222 (0.258, 19.158)	0.468
Subtotal	7/2	1.850 (0.216, 15.864)	0.575
Severe GE			
MIC	5/2	0.929 (0.698, 1.238)	0.615
Subtotal	7/2	0.832 (0.653, 1.061)	0.138
Case-control studies			
RVGE			
Hospitalization			
HIC	5/9	0.696 (0.349, 1.386)	0.302
MIC	17/4	0.881 (0.649, 1.195)	0.415
LIC	2/2	1.842 (0.388, 8.747)	0.442
Subtotal	24/15	1.264 (0.866, 1.844)	0.225
Severe RVGE			
MIC	10/2	1.097 (0.668, 1.800)	0.630
LMIC/LIC	10/3	0.885 (0.575, 1.362)	0.577
Subtotal	11/3	0.944 (0.603, 1.476)	0.799

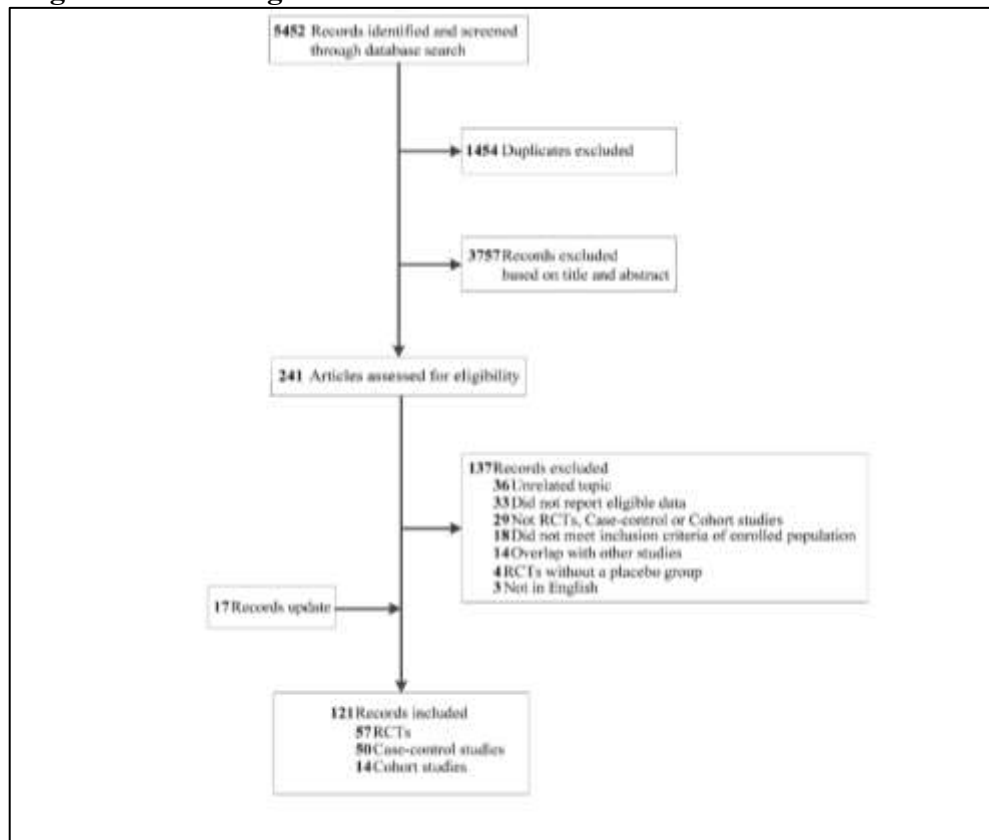
eTable 14. Indirect Comparisons between Different Vaccines in the Same Region

Region	Income	Study design	Vaccine (No. of studies)	RR or OR (95% CI)	p-value
The USA	HIC	RCT	RV1/RV5 (1/2)	0.894 (0.109, 7.310)	0.916
		Case-control	RV1/RV5 (2/7)	1.427 (0.853, 2.387)	0.716
Japan	HIC	RCT	RV1/RV5 (1/1)	0.825 (0.299, 2.275)	0.710
		Case-control	RV1/RV5 (2/2)	1.076 (0.620, 1.868)	0.794
Taiwan, China	HIC	RCT	RV1/RV5 (1/1)	0.383 (0.189, 77.638)	0.381
China	UMIC	RCT	RV1/RV5 (1/1)	0.953 (0.539, 1.684)	0.867
Spain	HIC	Case-control	RV1/RV5 (1/1)	1.076 (0.535, 2.166)	0.837
Bangladesh	LMIC	RCT	RV1/RV5 (1/1)	0.482 (0.192, 1.209)	0.120
Guatemala	LMIC	Case-control	RV1/RV5 (2/1)	0.836 (0.442, 1.580)	0.581
India	LMIC	RCT	Rotavac/Rotasiil (1/1)	0.916 (0.689, 1.217)	0.544

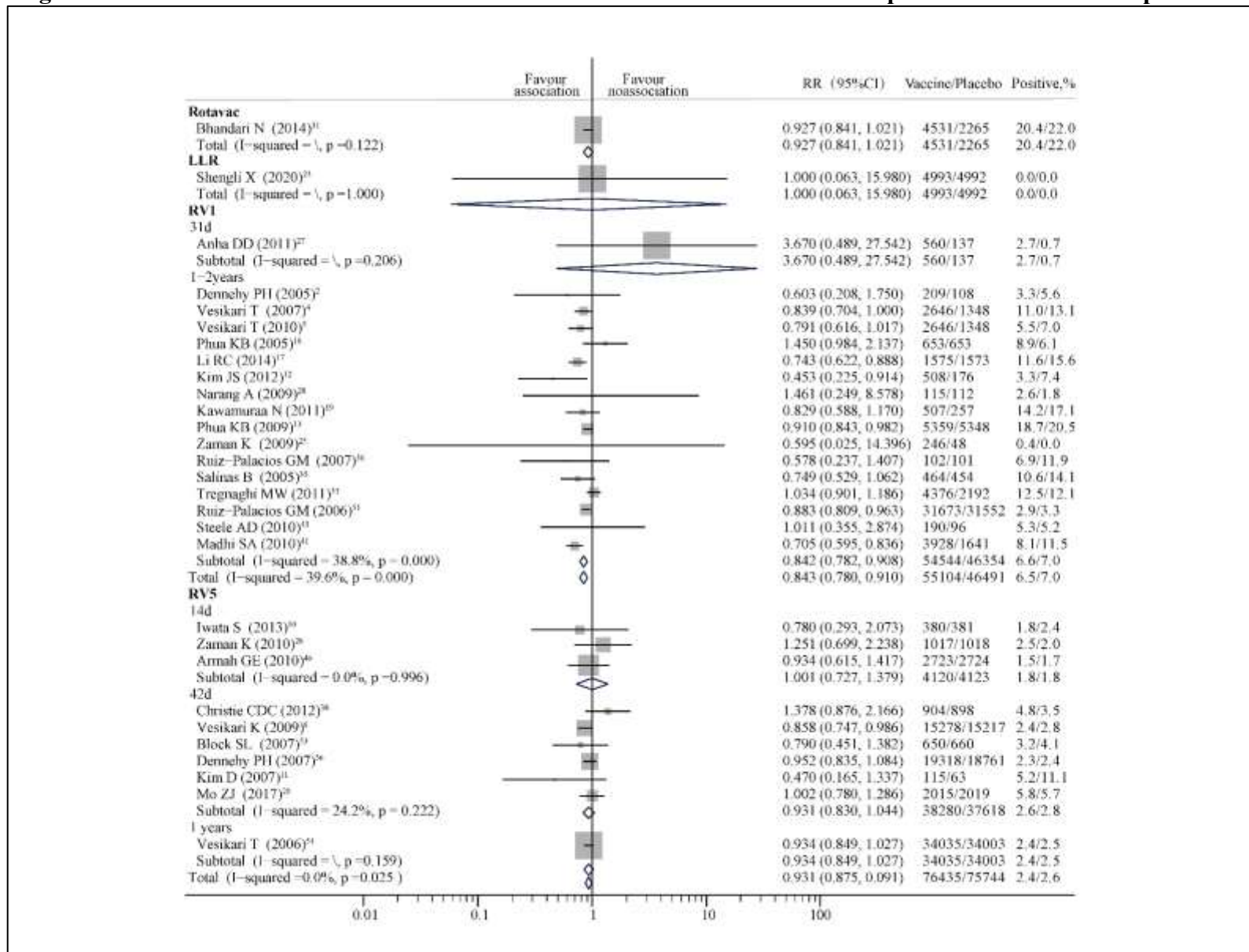
eTable 15. Random-effect Model of Strain-specific Rotavirus Vaccine Protection

	SRVGE		RCTs		Case-control studies		Cohort studies
			RVGE		RVGE Hospitalization and ED visits		RVGE
	RV1	RV5	RV1	RV5	RV1	RV5	RV1
G1P[8]	0.248 (0.139, 0.444)	\	0.526 (0.307, 0.899)	\	0.108 (0.057, 0.221)	0.156 (0.091, 0.268)	0.276 (0.096, 0.794)
G3P[8]	0.211 (0.067, 0.671)	\	0.043 (0.003, 0.736)	\	0.315 (0.202, 0.490)	\	\
G4P[8]	0.405 (0.168, 0.975)	\	\	\	0.080 (0.013, 0.479)	\	\
G8P[8]	\	\	\	\	\	\	0.105 (0.024, 0.465)
G9P[8]	0.151 (0.087, 0.261)	\	0.200 (0.023, 1.708)	\	0.411 (0.230, 0.736)	0.262 (0.145, 0.475)	0.908 (0.477, 1.727)
G12P[8]	\	\	\	\	\	\	0.441 (0.272, 0.713)
G1P[4]	0.200 (0.023, 1.708)	\	0.222 (0.048, 1.026)	\	\	\	\
G2P[4]	0.333 (0.191, 0.581)	\	0.411 (0.289, 0.585)	\	0.289 (0.185, 0.450)	0.060 (0.014, 0.252)	0.490 (0.107, 2.236)
G9P[6]	\	\	\	\	0.163 (0.056, 0.475)	\	\
G12P[6]	\	\	\	\	\	\	0.598 (0.272, 1.316)
G1	0.157 (0.064, 0.383)	0.281 (0.060, 1.313)	0.250 (0.119, 0.527)	0.253 (0.199, 0.321)	0.229 (0.120, 0.436)	0.243 (0.093, 0.634)	\
G2	0.187 (0.066, 0.533)	0.627 (0.375, 1.048)	0.394 (0.206, 0.752)	0.336 (0.143, 0.790)	0.336 (0.137, 0.823)	0.272 (0.106, 0.694)	\
G3	0.088 (0.032, 0.241)	0.337 (0.107, 1.058)	0.136 (0.058, 0.322)	0.429 (0.072, 2.561)	0.690 (0.420, 1.136)	0.184 (0.096, 0.354)	\
G4	0.046 (0.006, 0.356)	0.124 (0.033, 0.463)	0.353 (0.077, 1.619)	0.428 (0.121, 1.510)	\	0.056 (0.008, 0.377)	\
G8	0.222 (0.021, 2.373)	0.125 (0.016, 0.995)	\	\	\	\	\
G9	0.198 (0.126, 0.313)	0.226 (0.069, 0.739)	0.296 (0.213, 0.411)	0.331 (0.203, 0.539)	1.002 (0.672, 1.494)	0.221 (0.096, 0.507)	\
G12	0.474 (0.232, 0.967)	0.333 (0.014, 8.175)	\	\	0.400 (0.107, 1.496)	0.234 (0.066, 0.828)	\
P[4]	0.196 (0.023, 1.669)	0.727 (0.403, 1.313)	0.251 (0.023, 2.755)	\	\	0.272 (0.166, 0.447)	\
P[6]	0.438 (0.200, 0.959)	0.509 (0.312, 0.830)	\	\	0.747 (0.439, 1.270)	0.014 (0.001, 0.297)	\
P[8]	0.295 (0.126, 0.687)	0.436 (0.248, 0.765)	0.244 (0.152, 0.393)	0.309 (0.208, 0.461)	0.777 (0.513, 1.176)	0.385 (0.206, 0.718)	\

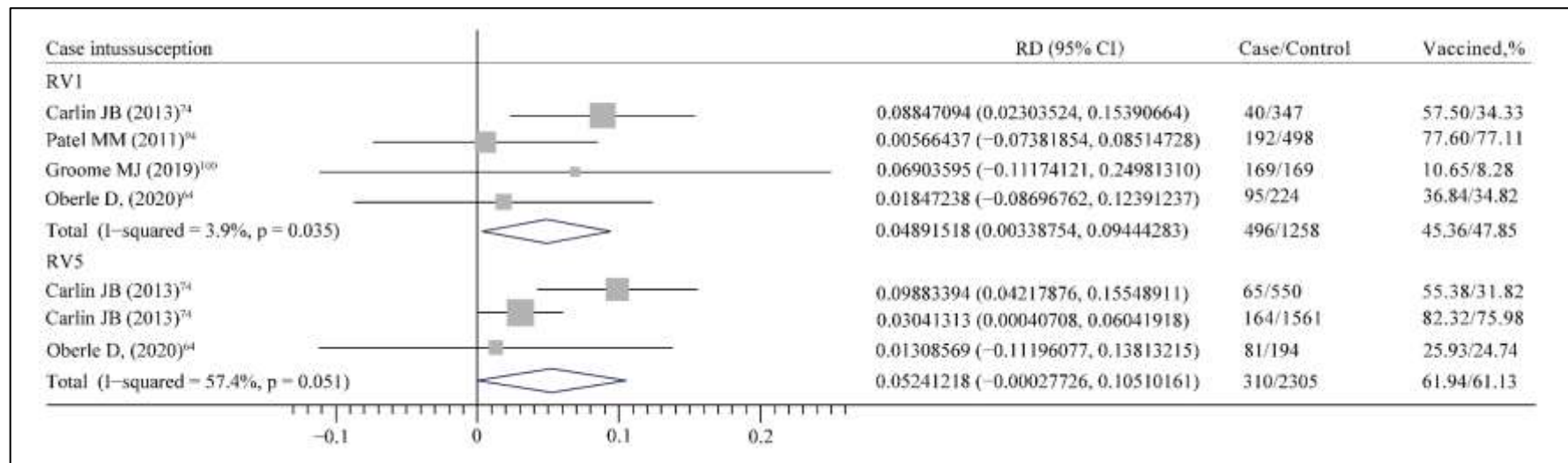
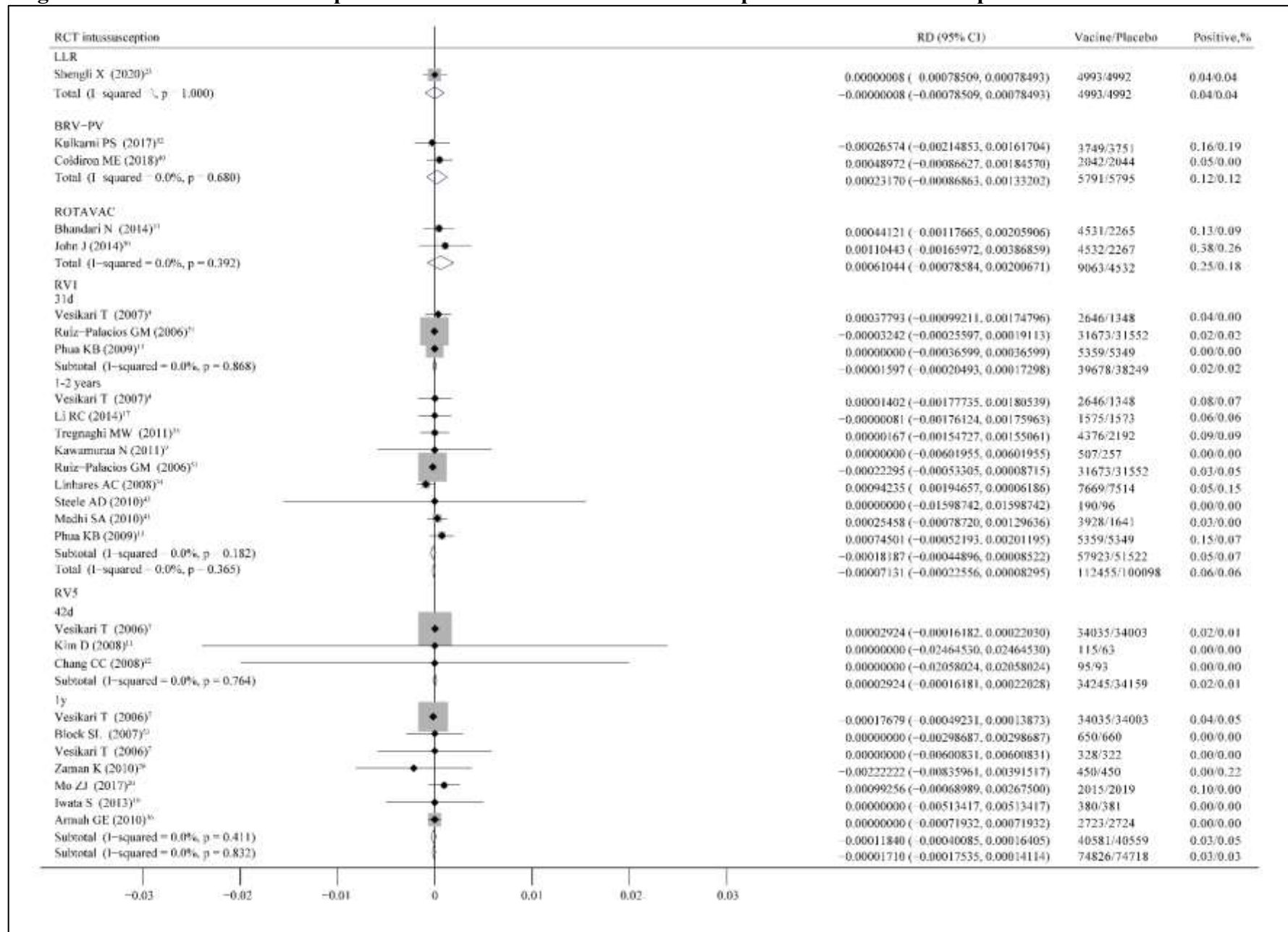
eFigure1. Flow Diagram



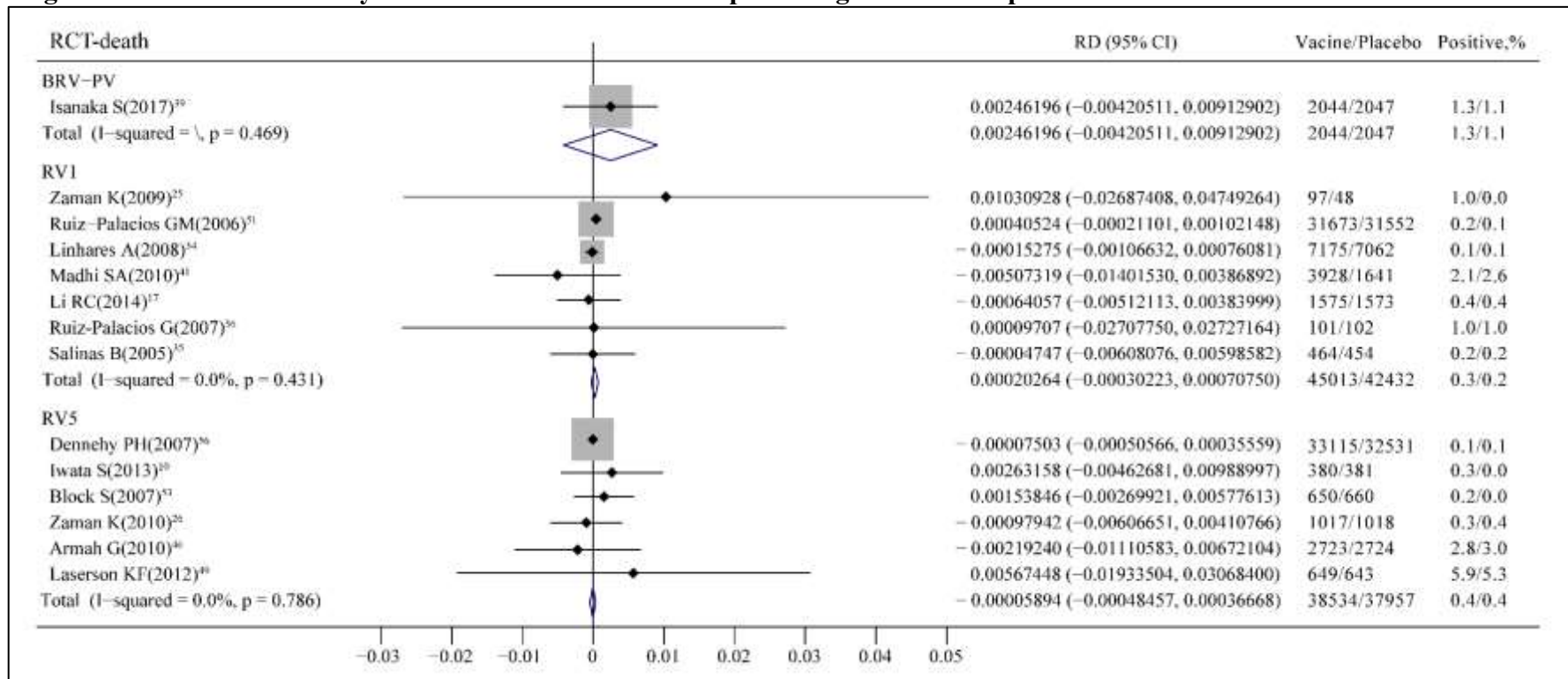
eFigure 2. The Risk of Serious Adverse Events Between Vaccine and Placebo Groups at Different Follow-up Times



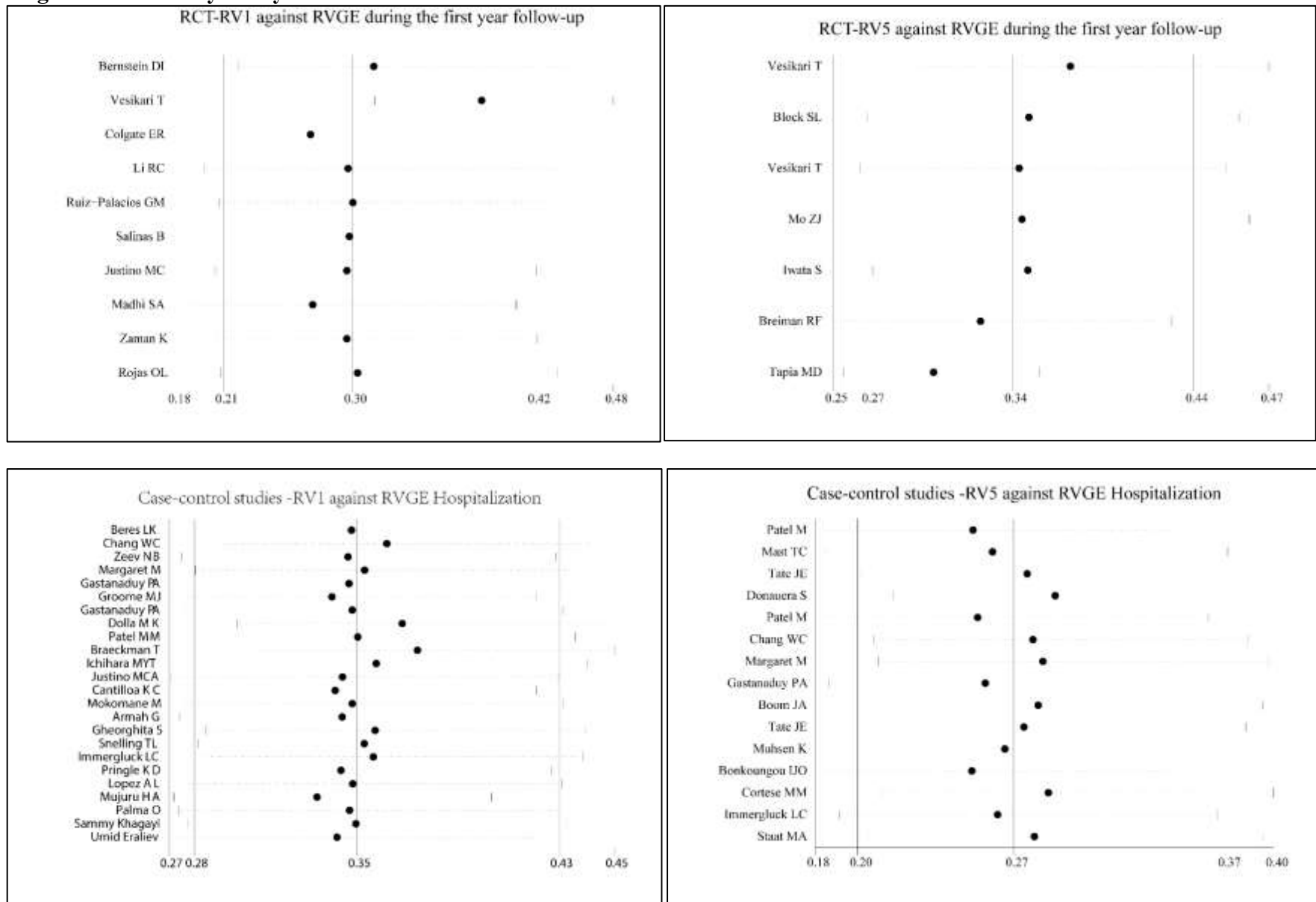
eFigure 3. The Risk of Intussusception Between Vaccine and Placebo Groups at Different Follow-up Times



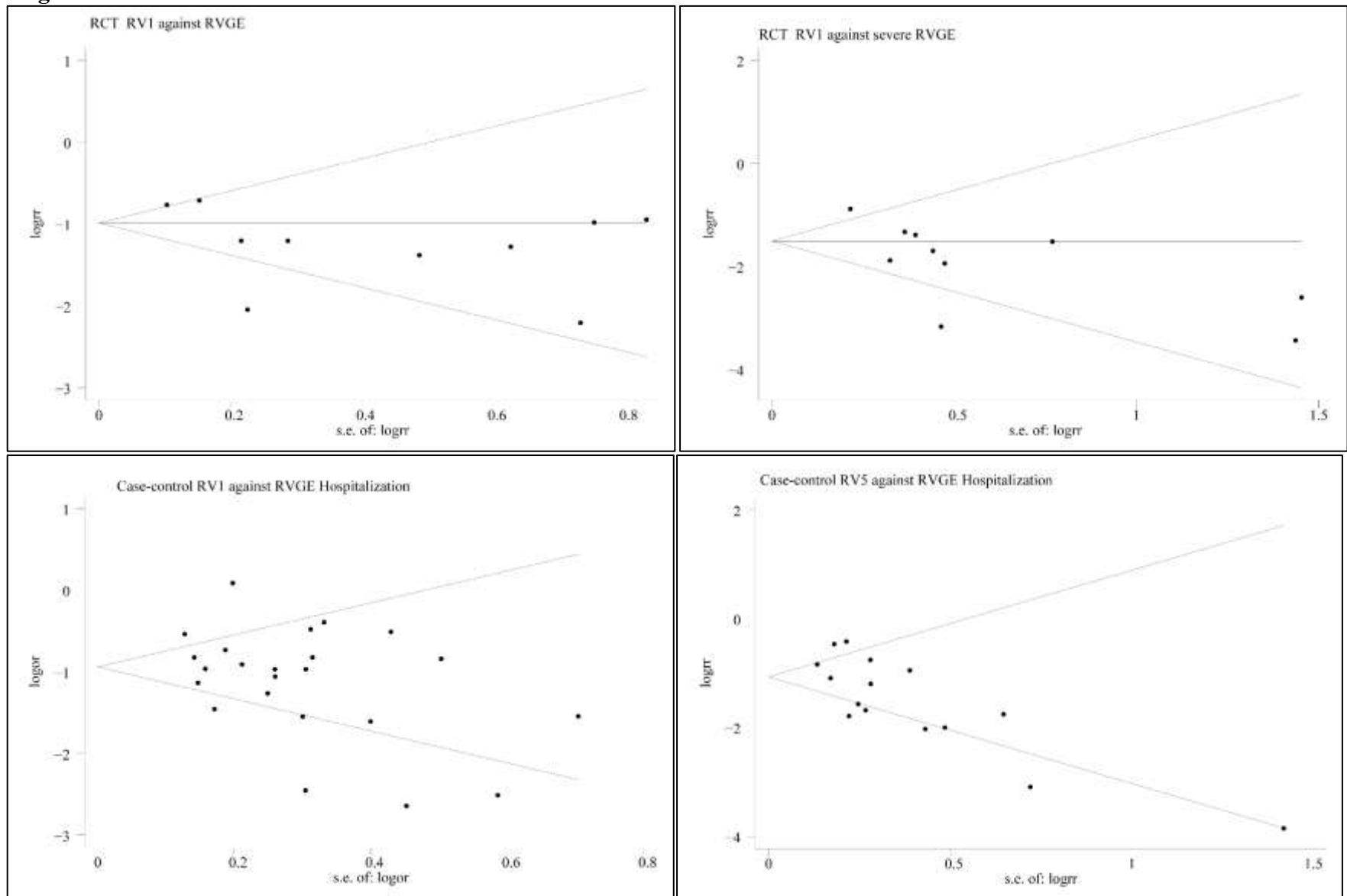
eFigure 4. All-Cause Mortality in Vaccine and Placebo Groups During the Follow-up Period



eFigure 5. Sensitivity Analyses



eFigure 6. Funnel Plots



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