Int J Clin Exp Med 2016;9(2):1306-1313
www.ijcem.com /ISSN:1940-5901/IJCEM0014327

Original Article

Risk of intussusception after rotavirus vaccination: a meta-analysis

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Received August 11, 2015; Accepted November 16, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Background: Rotavirus vaccines (RVs) are commonly used in children in the clinical setting. However, increasing concerns on its association with intussusception have been reported, with controversial outcomes. Methods: We conducted a comprehensive literature search of Medline, Pubmed and Embase. Children less than one year old vaccinated with RV1 and/or RV5 rotavirus vaccine were used as inclusion criteria. Results: 8 studies were included in the meta-analysis. Vaccines under studies were RV1 and RV5. Overall, there was an association between immunization and risk for developing intussusception: the overall estimate of relative risk (RR) of intussusception during the 7 days after dose 1 and/or dose 2 of RV1 and/or RV5 respectively was: 5.31 (95% confidence interval (CI): 3.22-8.74), P < 0.0001; 1.93 (95% CI: 1.43-2.61), P < 0.0001; 4.56 (95% CI: 3.05-6.82), P < 0.0001; 1.69 (95% CI: 1.18-2.40), P = 0.004. Sensitivity analysis showed that the significances of pooled estimates of RR stay unchanged when a single study was excluded for both vaccines and two doses. Conclusions: There is a significant increased risk of developing intussusception after immunization with RV during the first 7 days. Similarly increased risk pattern of intussusception for both vaccines are found where post-dose 1 has more risk compared to post-dose 2.

Keywords: Intussusception, rotavirus, relative risk, vaccination

Introduction

Rotavirus is the leading cause of acute gastroenteritis all worldwide, responsible in recent estimates for 200000 deaths and 10 million episodes of severe diarrhea annually among children below 5 years old [1-3]. In 1999, the first licensed vaccine, a rhesus-human reassortant (RRV-TV; RotaShied; Wyeth-Lederle) was withdrawn from use when found to be associated with an attributable risk of intussusception of about 1 in 10000 recipients after the first dose in infants 2 months of age or older [4].

Since 2005, two new oral rotavirus vaccines (RVs), a pentavalent human-bovine reassortant (RV5; RotaTeq; Merck) and a monovalent human rotavirus vaccine (RV1; Rotarix; GSK), have been widely licensed [5]. In 2009, the World Health Organization recommended routine rotavirus vaccination for all infants worldwide. In light of the experience with RRV-TV, the World Health Organization recommends that countries implementing rotavirus vaccination should conduct post marketing surveillance to identify rare or unexpected adverse events, including intussusception.

Studies of the association between intussusception and RV5 and RV1 have been published from the United States [6, 7], Latin America [8], Asia [9] and Australia [5, 10]. Evidence of an association between intussusception and RV1 was found in Mexico [8] and Australia [5]. For RV5, evidence of an association was reported in Australia [10] and United States [7]. These studies may be different in terms of design and population exposure, but all provided an estimate of intussusception risk during the first 7-day period after RV1 and/or RV5 vaccination.

The aim of this study was therefore to perform a systematic review and meta-analysis to evaluate the association between intussusception and receipt of either the RV1 or RV5 vaccine in the first 7 days post dose 1 and dose 2.

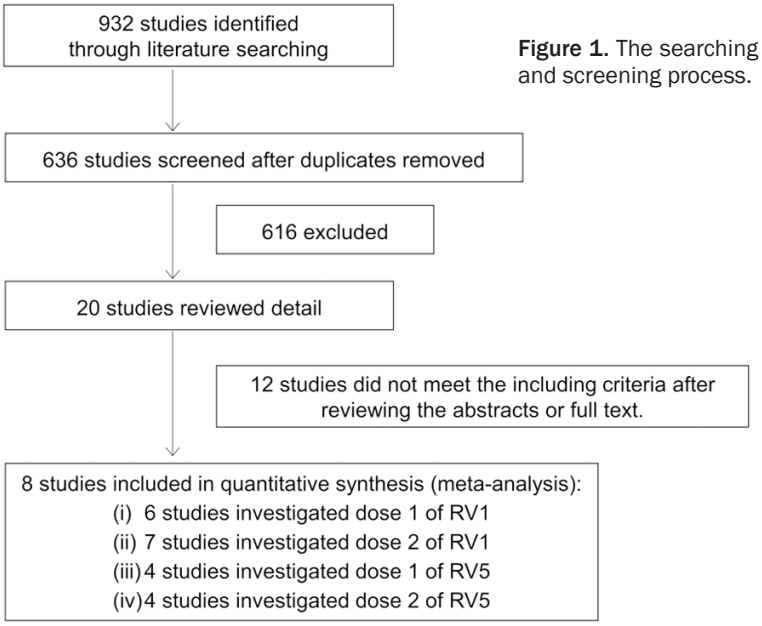

Figure 1. The searching and screening process.

Materials and methods

Literature search

A computerized search of the literature was conducted using: intussusception, rotavirus and vaccination through Medline, Pubmed and Embase in the English language. In addition, we searched abstracts of selected paper reviews from 2000 to 2015. References from relevant studies and previous reviews were also searched. The two authors independently screened all the studies and selected the articles that satisfied the eligibility criteria. The data was extracted onto a standardized data extraction sheet by one of the authors and checked independently by the second author. Disagreements were solved by checking the articles and contacting authors when needed.

Study selection

Studies and abstracts investigating the relationship between rotavirus vaccination and subsequent risk for development of intussusception were reviewed. Only self-controlled case series (SCCS) and self-controlled risk interval (SCRI) studies investigating the risk for intussusception after vaccination for infants under 1 year old were eligible for inclusion. Other criteria included: (1) Postlicensure studies; (2) Risk was estimated within 7 days after vaccination; (3) Risk was estimated for dose 1 and dose 2 separately; (4) Data was obtained through confirmed intussusception cases; (5) Full statistical report available for analysis. Thus, studies had to be excluded once one of the following criteria existed: (1) Studies with other risk periods (1-14, 1-21, 1-30, 8-14, 15-21 or 8-21 days); (2) Directly or indirectly relative risk (RR) and 95% confidence interval (CI) cannot be providedfor dose 1 or 2; (3) Articles with no or ambiguous case in risk or control period.

Outcomes

The primary outcome assessed was intussusception risk in patients receiving RV1 after dose 1; The second outcome assessed was intussusception risk in patients receiving RV1 after dose 2; The third outcome assessed was intussusception risk in patients receiving RV5 after dose 1; The forth outcome assessed was intussusception risk in patients receiving RV5 after dose 2.

Statistical methods

Pooled results were expressed as RR of intussusception with rotavirus vaccination, with 95% CI. The Pooled RR is calculated through combining each of the log-transformed RRs via the inverse variance method. Analyses were performed if at least three studies evaluating the same vaccination could be combined. Each meta-analysis was performed using only SCCS or SCRI. Heterogeneity among the studies included was assessed using I^2 statistic. The I^2 was defined as follows: 0-24% as good homogeneity; 25-50% as reasonable heterogeneity; 50-74% as large heterogeneity and 75-100% as extreme heterogeneity. If the statistic indicated heterogeneity existed, a random-effects model of analysis was used. Otherwise, a fixed-effects model of analysis was used. Separate analyses were performed for RV1 and RV5. For each vaccine, the pooled relative risk of intussusception was estimated after dose 1 and dose 2. Results were pooled using either fixed or random effect model depending on the results of heterogeneity test. Pooled RRs were calculated and two-sided $P < 0.05$ was considered to indicate statistical significance. Sensitivity analysis was

Table 1. Characteristics of studies included in the meta-analysis

Study	Country	Vaccine	Risk period (days)	Study design	Case number (Risk period *vs.* control)	Relative risk with 95% CI
Velázquez et al., 2012 [12]	Mexico	RV1	0-6	SCCS	Dose 1: 56 *vs.* 599	Dose 1: 6.49 (4.17, 10.09)
					Dose 2: 36 *vs.* 328	Dose 2: 1.29 (0.8, 2.11)
Haber et al., 2008 [6]	US	RV5	3-7	SCRI	Dose 1: 50 *vs.* 10	Dose 1: 3.75 (1.90, 7.39)
					Dose 2: 42 *vs.* 22	Dose 2: 1.43 (0.85, 2.4)
Yung et al., 2015 [9]	Singapore	RV1	1-7	SCCS	Dose 1: 2 *vs.* 18	Dose 1: 8.36 (2.42, 28.96)
					Dose 2: 1 *vs.* 17	Dose 2: 3.09 (0.41, 23.37)
Quinn et al., 2014 [10]	Australia	RV1	1-7	SCCS	Dose 1: 3 *vs.* 99	Dose 1: 11.1 (2.6, 47.38)
					Dose 2: 5 *vs.* 97	Dose 2: 4.0 (1.3, 12.31)
Escolano et al., 2015 [11]	Worldwide	RV5	3-7	SCCS	Dose 1: 19 *vs.* 48	Dose 1: 3.45 (1.84, 6.55)
					Dose 2: 34 *vs.* 60	Dose 2: 1.63 (0.86, 3.13)
Carlin et al., 2013 [5]	Australia	RV1	1-7	SCCS	Dose 1: 5 *vs.* 97	Dose 1: 6.76 (2.4, 19.01)
					Dose 2: 5 *vs.* 97	Dose 2: 2.84 (1.1, 7.34)
		RV5			Dose 1: 7 vs. 99	Dose 1: 9.89 (3.7, 26.42)
					Dose 2: 6 vs. 99	Dose 2: 2.81 (1.16, 6.8)
Yih et al., 2014 [7]	US	RV1	1-7	SCRI	Dose 1: 1 vs. 0	Dose 1: NA*
					Dose 2: 2 vs. 2	Dose 2: 3.5 (0.5, 25.1)
		RV5			Dose1: 5 vs. 3	Dose 1: 9.1 (2.2, 38.6)
					Dose 2: 3 vs. 6	Dose 2: 1.8 (0.4, 7.2)
Patel et al., 2011 [8]	Mexico	RV1	1-7	SCCS	Dose 1: 24 vs. 250	Dose 1: 5.3 (3, 9.3)
					Dose 2: 13 vs. 235	Dose 2: 1.8 (0.9, 3.8)
	Brazil				Dose 1: 4 vs. 317	Dose 1: 1.1 (0.3, 3.3)
					Dose 2: 21 vs. 279	Dose 2: 2.6 (1.3, 5.2)

*Not available since no case in control period.

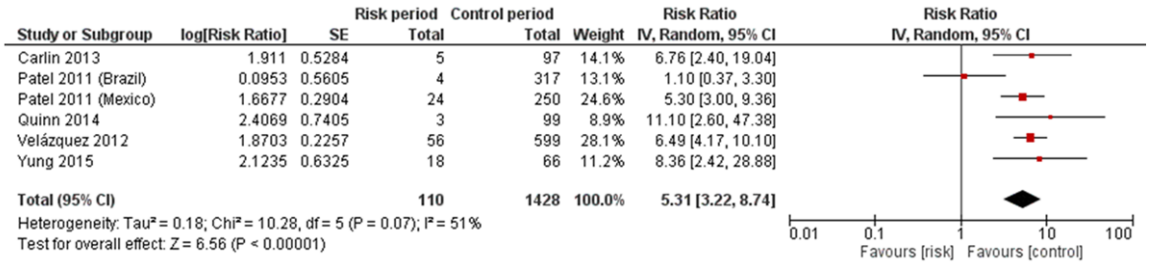

Figure 2. Forest plot for risk of intussusception after dose 1 of RV1.

Table 2. Sensitivity analysis for risk of intussusception after dose 1 of RV1

Study excluded	Overall RR	95% CI of RR	*P*-value
Carlin et al., 2013 [5]	5.07	(2.81, 9.15)	< 0.0001
Patel et al., 2011 [8] (Brazil)	6.38	(4.67, 8.73)	< 0.0001
Patel et al., 2011 [8] (Mexico)	5.27	(2.62, 10.61)	< 0.0001
Quinn et al., 2014 [10]	4.92	(2.88, 8.43)	< 0.0001
Velázquez et al., 2012 [12]	4.94	(2.45, 9.98)	< 0.0001
Yung et al., 2015 [9]	4.98	(2.83, 8.76)	< 0.0001

performed for all outcomes. We intended to assess publication bias using funnel plot techniques and Begg's rank test, as appropriate given the known limitations of these methods.

All statistical analyses were performed using Reviewer Manager 5.3 (RevMan, Denmark).

Results

Study characteristics

A total of 932 studies were identified through database searching and reference mining of review articles and relevant publications. There are 636 studies screened after duplicates were removed. Following screening of titles and abstracts, 616 studies were excluded. 20 studies [5-24] were included and

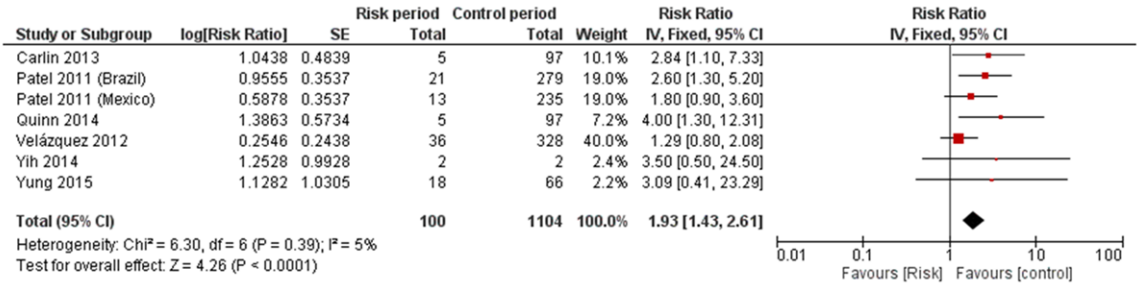

Figure 3. Forest plot for risk of intussusception after dose 2 of RV1.

Table 3. Sensitivity analysis for risk of intussusception after dose 2 of RV1

Study excluded	Overall RR	95% CI of RR	*P*-value
Carlin et al., 2013 [5]	1.85	(1.34, 2.54)	0.0002
Patel et al., 2011 [8] (Brazil)	1.80	(0.9, 3.6)	0.0006
Patel et al., 2011 [8] (Mexico)	1.96	(1.4, 2.74)	< 0.0001
Quinn et al., 2014 [10]	1.82	(1.33, 2.49)	< 0.0002
Velázquez et al., 2012 [12]	2.52	(1.71, 3.72)	< 0.0001
Yung et al., 2015 [9]	1.91	(1.41, 2.59)	< 0.0001
Yih et al., 2014 [7]	1.90	(1.4, 2.58)	< 0.0001

reviewed in detail. Of these, 12 studies were excluded based on the inclusion criteria. Thus, the rest eight studies [5-12] were included in the quantitative synthesis (**Figure 1**). For these eight studies, either relative incidence rates or relative risk is reported. For this meta-analysis, we considered both as estimates of the relative risk for intussusception after vaccination. Most studies reported relative risk of intussusception from day 1 to day 7 after vaccination while two of the studies [6, 11] reported risk in 3-7 days after vaccination and one study [12] reported relative risk in 0-6 days. In this meta-analysis, we consider them all as relative risk in first 7-day period. The studies included are summarized in **Table 1**.

Risk of intussusception after dose 1 of RV1

Seven studies investigated the risk of developing intussusception after RV1 vaccination. However, one study [7] was excluded for this analysis since an infinite value was reported as the relative risk (no case in control period). Six studies were therefore included in the meta-analysis of this outcome. After pooling of data, significant heterogeneity among the studies was found. Therefore we used a random-effects model for analysis. The pooled estimates (RR = 5.31, 95% CI: 3.22-8.74, P < 0.00001, I^2 = 51%) showed RV1 significantly increases intussusception risk in a 7-day period after dose 1 (**Figure 2**). Sensitivity analysis excluding the study one by one did not change the significance of overall estimate (**Table 2**).

Risk of intussusception after dose 2 of RV1

Seven studies which investigated the risk of developing intussusception after RV1 vaccination were included in the meta-analysis of the second outcome. After pooling of data, there was no significant heterogeneity among the studies found. Therefore we used a fixed-effects model for analysis. The pooled estimates (RR = 1.93, 95% CI: 1.43-2.61, P < 0.0001, I^2 = 5%) showed RV1 significantly increases intussusception risk in a 7-day period after dose 2 (**Figure 3**). Sensitivity analysis excluding the study one by one did not change the significance of pooled estimate (**Table 3**).

Risk of intussusception after dose 1 of RV5

Four studies which investigated the risk of developing intussusception after RV5 vaccination were included in the meta-analysis of the third outcome. After pooling of data, there was found to be no significant heterogeneity among the studies. Therefore we used a fixed-effects model for analysis. The pooled estimates (RR = 4.56, 95% CI: 3.05-6.82, P < 0.00001, I^2 = 31%) showed RV5 significantly increases intussusception risk in a 7-day period after dose 1 (**Figure 4**). Sensitivity analysis excluding the study one by one did not change the significance of pooled estimate (**Table 4**).

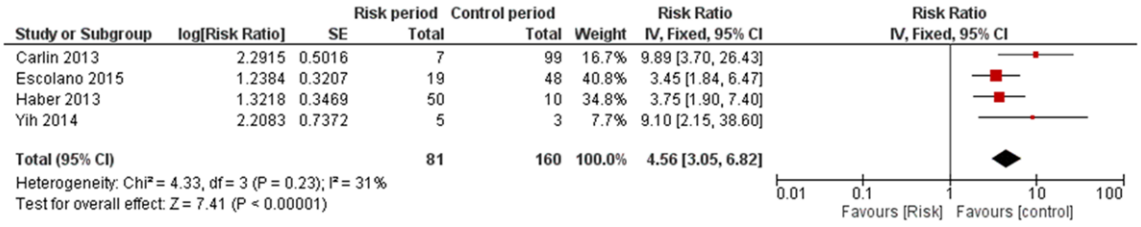

Figure 4. Forest plot for risk of intussusception after dose 1 of RV5.

Table 4. Sensitivity analysis for risk of intussusception after dose 1 of RV5

Study excluded	Overall RR	95% CI of RR	*P*-value
Carlin et al., 2013 [5]	3.91	(2.52, 6.07)	< 0.0001
Escolano et al., 2015 [11]	5.53	(3.28, 9.32)	< 0.0001
Haber et al., 2008 [6]	5.07	(3.08, 8.33)	< 0.0001
Yih et al., 2014 [7]	4.31	(2.84, 6.54)	< 0.0001

Risk of intussusception after dose 2 of RV5

Four studies which investigated the risk of developing intussusception after RV5 vaccination were included in the meta-analysis of the fourth outcome. After pooling of data, there was found to be no significant heterogeneity among the studies. Therefore, we used a fixed-effects model for analysis. The pooled estimates (RR = 1.69, 95% CI: 1.18-2.4, P = 0.004, I^2 = 0%) showed RV5 significantly increases intussusception risk in a 7-day period after dose 2 (**Figure 5**). Sensitivity analysis excluding the study one by one did not change the significance of pooled estimate (**Table 5**).

Publication bias

We performed the funnel plot to test the publication bias using the risk of intussusception after dose 2 of RV1 as the example (**Figure 6**). The graph showed both sides were almost symmetrical, which suggested that the data of the current study had no significant publication bias. Moreover, the results of Begg's test also supported our conclusion (*P*-value of dose 1 and/or dose 2 of RV1 and/or RV5 respectively was 0.71, 0.65, 0.31, 0.31).

Discussion

Intussusception is among the most common abdominal emergencies among young children [25-27]. Intussusception is a medical condition in which a part of the intestine invaginates (folds into) into another section of intestine, similar to the way the parts of a collapsible telescope slide into one another [28]. With early diagnosis, appropriate fluid resuscitation, and therapy, the mortality rate from intussusception in children is less than 1%. If left untreated, however, this condition is uniformly fatal in 2-5 days [29]. The causes of intussusception are not fully understood, yet, there is evidence linking recent episodes of gastroenteritis and increased risk of intussusception [30, 31]. Adenovirus was repeatedly recovered in higher proportions from fecal samples of patients with intussusception compared with control children [32], however no association has been found between natural rotavirus infection and intussusception [33-35]. In this study, we performed a systematic review and meta-analysis to evaluate the association between intussusception and receipt of either RV1 or RV5 vaccine in the first 7 days post dose 1 and dose 2.

Including 8 studies with study designs of self-controlled case series and risk interval, we performed a meta-analysis of the risk of developing intussusception after rotavirus vaccination. Of note, all these studies included focused only on infant vaccination. Overall, our results showed significant increased risk of developing intussusception after immunization with rotavirus vaccine for both RV1 and RV5 for a 7-day period post vaccination of dose 1 and dose 2. When we performed sensitivity analyses excluding the study one by one, we did not find any inconsistent result.

The results of this meta-analysis indicated the risk of developing intussusception after infant rotavirus vaccination. The strength of our study is the large number of patients included in the meta-analysis. Limitations of our work are mainly due to the fact that studies investigating the risk of developing intussusception after rotavirus vaccination were not always homoge-

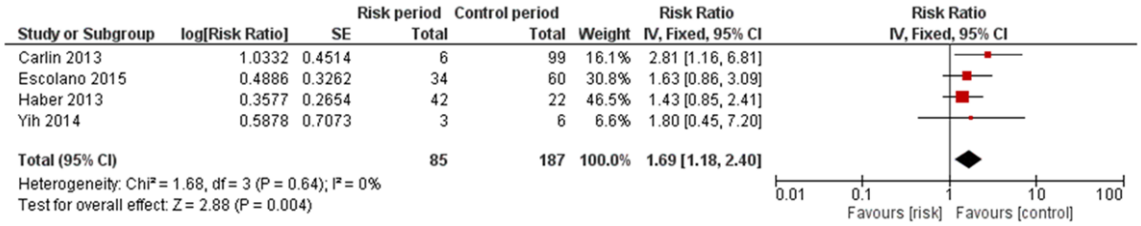

Figure 5. Forest plot for risk of intussusception after dose 2 of RV5.

Table 5. Sensitivity analysis for risk of intussusception after dose 2 of RV5

Study excluded	Overall RR	95% CI of RR	*P*-value
Carlin et al., 2013 [5]	1.53	(1.16, 6.81)	0.03
Escolano et al., 2015 [11]	1.71	(1.12, 2.62)	0.01
Haber et al., 2008 [6]	1.94	(1.2, 7.2)	0.0007
Yih et al., 2014 [7]	1.68	(1.16, 2.42)	0.0006

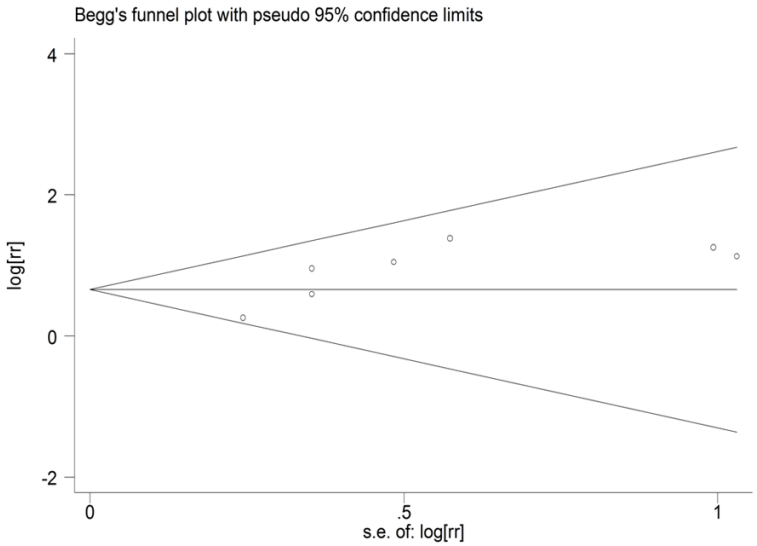

Figure 6. Funnel plot of risk of intussusception after dose 2 of RV1.

neous regarding their study design, sample size, and/or geographic location. Indeed, we found a significant heterogeneity among the studies for RV1 vaccine after dose 1. Another limitation is, the small number of studies for two vaccines did not allow us to explore further publication bias and heterogeneity.

We are fully aware of the limitations of a meta-analysis of mostly observational studies, and that interpretation of overall results should be considered with caution. Association between rotavirus vaccine and risk for intussusception should be analyzed cautiously because of study heterogeneity and will require further investigation.

In conclusion, our analysis indicates that the two currently licensed rotavirus vaccines give temporal rise (within 7-day period) to a small but measurable increase in the incidence of intussusception in young infants. Despite a small increased risk of intussusception associated with both RV1 and RV5, the benefits of rotavirus vaccination in preventing rotavirus gastroenteritis should be considered and balanced. Countries planning to introduce rotavirus vaccines will need to consider their rotavirus disease burden in relation to the incidence of intussusception and the ability to diagnosis and treat.

Acknowledgements

This study received financial support from National Key Clinical Specialty Construction Programs of China (2014-2016), National Natural Science Foundation of China (No. 81370-472, No. 81300517 and No. 81401243), Shanghai City Health Bureau for Youth Scientific Fund Project (No. 20134y100), Shanghai Rising-Star Program (A type) (No. 15QA-1400800) and The Science Foundation of Shanghai (No. 11JC1401300, No. 13ZR1451-800, No. 14ZR1404000, No. 14411969860 and 15ZR1404200).

Disclosure of conflict of interest

None.

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