World Health Organization

Global Vaccine safety
Essential Medicines & Health Products
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INFORMATION SHEET

OBSERVED RATE OF VACCINE REACTIONS

ROTAVIRUS VACCINE

June 2018

Types of vaccines

Rotaviruses are non-enveloped RNA viruses which are classified according to 2 surface proteins contained on the outer layer of the viral capsid - the VP7 (glycoprotein or G protein) and the VP4 (protease cleaved protein or P protein). The rotavirus strains are commonly referred to by their G type with G1, G2, G3, G4, and G9 accounting for 90% of virus types globally. Among P types found with these G types P[4], P[6], and P[8] are most prevalent [Kobayashi 2007].

A number of rotaviral vaccines have been developed that vary depending on the source of the virus and the virus types used. The currently prequalified oral rotaviral vaccines are live attenuated and include: Rotarix (GSK – referred to as RV1) an attenuated human virus of the G1P[8] strain which protects against non G1 serotypes on the basis of their common P[8] antigen; and RotaTeq (Merck – referred to as RV5) a pentavalent product with reassortant virus from human and bovine origin that express human serotypes G1, G2, G3, G4, and P[8]. Rotavac (Bharat) and Rotasiil (Serum Institute of India) vaccines are currently in the pipeline. (See Table 1).

Table 1

Name	Vaccine antigens	Excipients
Rotarix (GSK)	Attenuated human strain R1X4414 of G1P[8] strain	Sucrose, dextran 40, sorbitol, amino acids, Dulbecco's modified eagle medium, calcium carbonate, xanthum gum. Calcium carbonate buffer as diluent.
RotaTeq (CSL/Merck)	Pentavalent rotavirus reassortant with human G1, G2, G3, G4 and P[8]	Sucrose, sodium citrate, sodium phosphate, sodium hydroxide, polysorbate 80, cell culture media, trace amounts of fetal bovine serum.
Rotavac (Bharat)	Monovalent vaccine containing live attenuated Rotavirus 116E	Sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, culture media.
Rotasiil (Serum Institute of India)	Live Attenuated Bovine - Human Rotavirus Reassortant [G1, G2, G3, G4 and G9 grown on vero cells] 10 5.6 FFU / Serotype	Eagle's MEM (Minimum Essential Medium) with Hank's Salts, Glutamine and Sodium bicarbonate. Sucrose and Glycine.

Safety summary and information sheet

Over half of the countries in the world now include rotavirus vaccines in their national immunisation programmes [Ruiz-Palacios 2006]. Post-licensure surveillance data concerning the safety profiles for each of the rotavirus vaccine brands have detected no serious safety issues to date except rare reports of intussusception. The safety of the rotavirus vaccine has been regularly reviewed by the Global Advisory Committee for Vaccine Safety (GACVS) who have not identified any safety concerns: http://www.who.int/vaccine_safety/committee/topics/rotavirus/en/

This rotavirus information sheet was adapted from the earlier version first published in June 2012 following a systematic literature review, conducted in September 2017, which included available evidence on the serious adverse events associated with rotavirus vaccines.

A large body of randomised controlled trial evidence comprising over 80,000 participants provided data upon which the rates of serious adverse events were calculated. In addition, several large cohort studies provided evidence for specific adverse outcomes, predominantly intussusception. The specific methodology, articles' profiles and quality of evidence that comprise the systematic review can be accessed through http://www.who.int/vaccine_safety/publications/WHO_Rotavirus_vaccines_systematic_review_Cochrane.pdf.

Adverse events

Minor adverse events (See Table 2)

Local adverse events

A review of 31 RV1 and 12 RV5 studies examined occurrence of fever, diarrhea and vomiting at several timepoints: after the first, second, third doses, and at the end of follow-up period. There were no differences between the vacciens and placebo for each of these outcomes and timepoints [Soares-Weiser et al 2012).

Serious adverse events – systematic review (See Table 3)

A comprehensive systematic review containing a large body of high-certainty evidence consistently found no difference in the rate of serious adverse events (SAE) between people who have received either Rotarix, RotaTeq, Rotavac, or Rotasiil rotavirus vaccines and people who received a placebo or no intervention. A number of cohort studies found no relationship between exposure to rotavirus vaccination and development of intussusception and other SAEs.

The results of the analysis for the specific outcomes are summarised in Table 3 using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology http://www.gradeworkinggroup.org/.

Results are stratified by WHO mortality strata. Stratum A represents countries with very low child and adult mortality, stratum B are countries with low child and adult mortality, stratum C have low child but high adult mortality, stratum D have high adult and child mortality, and stratum E very high adult and high child mortality. Mortality strata are according to the World Health Organization list of member states, mortality rate for children ≤5 years per 1000 live births http://www.who.int/whr/2003/en/member_states_182-184_en.pdf

The outcomes from randomised controlled trials included SAEs and intussusception. A comparison of effects showed that there is little to no difference in the absolute event rate for SAEs in those vaccinated with RV1 or RV5 in all mortality strata compared with placebo.

For Rotavac and Rotasiil there was little to no difference in the absolute event rate for SAEs in those vaccinated compared to placebo in mortality stratum D (trials carried out in India [Rotavac and Rotasiil] and Niger [Rotasiil]).

Other vaccine safety issues

Intussusception with rhesus-human reassortant rotavius vaccine (Rotashield)

The first oral rotavirus vaccine was licensed in the United States of America was the rhesus-human reassortant tetravalent vaccine (Rotashield, RRV-TV: Wyeth Lederle Vaccines).

Pre-licensure trials demonstrated a possible association between vaccination and intussusception but because of the limited number of subjects included these trials no statistical association was established [Rennels et al. 1998]. Following widespread use of the vaccine a number of cases of intussusception were reported to the Vaccine Adverse Events Reporting System (VAERS) eventually leading to a suspension of vaccination. Subsequent studies demonstrated a causal relationship between vaccination and intussusception. Statistical significance was demonstrated for between 3 to 14 days following vaccination with the first dose of the vaccine (odds ratio 21.7) [Murphy et al. 2001].

The estimated incidence of intussusception following the Rotashield vaccine is thought to be 1 per 2,500-9,500 vaccinees, with the range depending on a number of factors which include the methods used to analyse the adverse event data, case definitions and the estimated baseline rates of intussusception [Murphy et al. 2003]. Importantly, no cases occurred in infants less than 2 months of age although 16% of all first doses were given at this age [Simonsen et al. 2005]. In the United States, intussusception rates vary markedly by age in the first year of life, with the lowest rates under 9 weeks of age, peaking at 62 per 100,000 infants among those 26 to 29 weeks of age, and then decreasing to 26 per 100,000 infants by 52 weeks of age [Tate et al. 2008].

As shown in Table 3, the current evidence on Rotarix, Rotateq, Rotasiil, and Rotavac vaccines shows no difference in the absolute event rate of intussusception up to two years following any rotavirus vaccination compared with placebo.

Other studies using different designs have noted a potential temporary increase in risk of intussusception in the first week following a dose of rotavirus vaccine [Stowe et al 2016].

Death

Deaths were reported in nearly every study, and there was no significant difference in the number of deaths between infants given rotavirus vaccines or placebo. Causes of deaths in all trials are listed in Appendix 1 of the WHO report http://www.who.int/vaccine_safety/publications/WHO_Rotavirus_vaccines_systematic_review_Cochrane.pdf.

Rotavirus vaccines in combination with other vaccines

There was little to no difference in the rate of SAEs when RV1 or RV5 was co-administered with other childhood vaccines compared with when there was no co-administration.

Age of vaccine administration

Because of the difference in background rates of intussuception due to age, more cases of intussusception would be expected among older infants than younger infants, even if the risk associated with rotavirus vaccine is the same across all ages. This has led to the current product labelling to administer the last scheduled dose of rotaviral vaccines prior to an upper age limit. This upper age limit varies according to type of vaccine used (For Rotarix the 2nd dose should be administered by the 25th week of age and for RotaTeq the third dose should be administered by the 33rd week of age). WHO recommends that the first dose of rotavirus vaccine be administered as soon as possible after 6 weeks of age, along with diphtheria-tetanus-pertussis (DTP) vaccination so as to ensure induction of protection prior to natural rotavirus infection DTP3) and facilitate reaching children who were previously excluded. Because of the typical age distribution of rotavirus gastroenteritis (RVGE), rotavirus vaccination of children >24 months of age is not recommended. [WHO 2013]. There are no safety data of administration of the vaccine beyond this

recommended age group and specifically whether administering the vaccine beyond this age is associated with an increased risk of intussusception.

Route of vaccine administration

The vaccine should not be injected.

Use in infants in households with pregnant women

There is no contraindication to the vaccine being administered to infants who share households with pregnant women.

Use in the immunocompromised

Limited evidence is available to date about vaccination in immunocompromised infants (acquired or primary). In one study, rates of adverse events in children infected with HIV were not increased compared with non-HIV-infected infants. Children with severe combined immunodeficiency syndrome (an uncommon condition affecting about 1 in 100,000 infants) who have been vaccinated have demonstrated prolonged shedding of the live attenuated vaccine virus strains [Patel et al 2009]. However, the benefit and risks of vaccination require additional assessment.

Use in preterm infants

Premature infants can be immunised at their chronological age. In one study of 2070 preterm infants (gestation median 34 weeks, range 25-36) there was no increase in adverse events in the vaccinated group [Goveia et al. 2007; Van den Wielen et al. 2008; Omenaca et al. 2012].

Use after blood transfusion

Ideally vaccination should not occur within 42 days of the administration of an antibody-containing blood product. However, if this would then preclude administration of the last dose of the vaccine then the vaccine should be given [American Academy of Pediatrics Committee on Infectious Diseases 2007].

Past history of intussusception

There is no information on the risk of vaccinating infants who have a past history of intussusception.

Kawasaki disease

Kawasaki disease following receipt of both vaccines a pre-licensure vaccine trial has been described in a small number of infants. However, it is unclear whether the rates observed among vaccinated infants are higher than expected in the normal population. Further studies are needed to investigate this potential association and given the current evidence a casual association is not thought to be likely [WHO 2009; Soares-Weiser et al. 2012].

The WHO vaccine reaction rates information sheets

WHO vaccine reaction rates information sheets are primarily designed for use by national public health officials and immunization programme managers, but this information may interest others. These sheets can be used for causality assessment of Adverse Events Following Immunization (AEFI) because they describe vaccine product related reactions. Also, this information may help in preparing communication materials. WHO has developed these rate sheets through a systematic process involving global vaccine safety and vaccine experts. For the reviews of serious adverse events, academics who specialize in systematic literature reviews and assessment of evidence quality using the GRADE process have been contracted. This material is then reviewed by GACVS (or a GACVS subcommittee) and also by the WHO Immunization, Vaccines and Biologicals division. GACVS approves the material before review by the WHO Assistant Director General's office.

Publications of the WHO vaccine reaction rates information sheets can be found at http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/. Information sheets are periodically reviewed on a need-based manner with newer vaccines being more frequently reviewed and updated than those established for many decades.

Details of minor and severe adverse reactions following immunization including the expected rates of vaccine reactions have been included when these are available in the published literature. Since published literature often does not distinguish between severe and serious AEFI, the terminologies used in this rate sheet have not considered them separately.

Table 2. Summary of minor adverse events – fever, diarrhea, and vomiting*

Outcome	Timepoint	Rotarix		RotaTeq	
		Participants (RCTs)	Relative Risk [95% CI]	Participants (RCTs)	Relative Risk [95% CI]
Fever	After dose 1	11,563 (20)	1.08 [0.98, 1.18]	3090 (3)	1.28 [1.04, 1.58]**
	After dose 2	11,156 (19)	0.98 [0.91, 1.06]	417 (1)	0.75 [0.47, 1.19]
	After dose 3	1390 (4)	0.98 [0.86, 1.13]	416 (1)	1.10 [0.77, 1.59]
	End of follow-up	8799 (16)	0.97 [0.93, 1.01]	14,067 (7)	1.03 [0.93, 1.15]
Diarrhea	After dose 1	14,103 (20)	1.01 [0.86, 1.20]	711 (1)	0.99 [0.71, 1.39]
	After dose 2	11,156 (19)	0.93 [0.76, 1.14]	-----	-----
	After dose 3	1390 (4)	0.69 [0.35, 1.36]	-----	-----
	End of follow-up	11,178 (15)	0.92 [0.80, 1.07]	12,763 (6)	1.04 [0.98, 1.12]
Vomiting	After dose 1	14,103 (20)	1.06 [0.96, 1.17]	711 (1)	0.87 [0.59, 1.29]
	After dose 2	11,156 (19)	0.92 [0.78, 1.09]	-----	-----
	After dose 3	1390 (4)	1.34 [0.71, 2.50]	-----	-----
	End of follow-up	11,178 (15)	0.93 [0.82, 1.05]	11,970 (5)	1.00 [0.91, 1.09]

*From Soares-Weiser et al. 2012 http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD008521.pub3/full

**There was a 28% increase in the incidence of fever after the first dose of Rotateq vaccine compared to placebo (rate in RotaTeq group: 1.9 per 1000 infants). There were no significant differences between vaccine and placebo groups for the other timepoints, or for diarrhea or vomiting.

RCT: randomized controlled trial; CI: confidence interval

Table 3. GRADE Summary of Findings Table (grading of quality of scientific evidence) for serious adverse events following RV vaccines*

Participants: Infants and children
Settings: Worldwide
Comparison: Rotarix, RotaTeq, Rotavac, or Rotasiil vs placebo or no intervention

Outcome	WHO mortality strata	Data size and source	Comparison of effects*		Size of effect	Certainty of the evidence (GRADE)
			Vaccine	Placebo		
Serious adverse events (1 month – 2 years follow up)	A	RV1 versus placebo: Based on data from 18,132 participants in 10 randomised controlled trials	3946 per 100,000	4336 per 100,000	No difference	⊕⊕⊕⊕ HIGH
			Difference: 390 fewer per 100,000 people vaccinated (1041 fewer to 434 more) Relative risk (95% CI): 0.91 (0.76 to 1.10)			
	B	RV1 versus placebo: Based on data from 79,960 participants in 16 randomised controlled trials	3757 per 100,000	4527 per 100,000	Slight decrease	⊕⊕⊕⊕ HIGH
			Difference: 770 fewer per 100,000 people vaccinated (272 to 1177 fewer) Relative risk (95% CI): 0.83 (0.74 to 0.94)			
	C	RV1 versus placebo: Based on data from 209 participants in 1 randomised controlled trial	4969 per 100,000	Not estimable	No difference	⊕⊕OO LOW
			Difference: 4969 more per 100,000 people vaccinated (0 to 0 fewer) Relative risk (95% CI): 5.14 (0.3 to 87.5)			
	D	RV1 versus placebo: Based on data from 64,742 participants in 4 randomised controlled trials	2889 per 100,000	3283 per 100,000	Slight decrease	⊕⊕⊕⊕ HIGH
			Difference: 394 fewer per 100,000 people vaccinated (131 to 624 fewer) Relative risk (95% CI): 0.88 (0.81 to 0.96)			
	E	RV1 versus placebo: Based on data from 5,964	9995 per 100,000	11,358 per 100,000	No difference	⊕⊕⊕⊕ HIGH

		participants in 4 randomised controlled trials	Difference: 1363 fewer per 100,000 people vaccinated (2726 fewer to 341 more) Relative risk (95% CI): 0.88 (0.81 to 0.96)			
Serious adverse events (1 month – 2 years follow up)	A	RV5 versus placebo: Based on data from 70,512 participants in 4 randomised controlled trials	2377 per 100,000	2556 per 100,000 Difference: 179 fewer per 100,000 people vaccinated (409 fewer to 51 more) Relative risk (95% CI): 0.93 (0.84 to 1.02)	No difference	⊕⊕⊕⊕ HIGH
	B	RV5 versus placebo: Based on data from 73,246 participants in 6 randomised controlled trials	3152 per 100,000	3318 per 100,000 Difference: 166 fewer per 100,000 people vaccinated (697 fewer to 465 more) Relative risk (95% CI): 0.95 (0.79 to 1.14)	No difference	⊕⊕⊕O MODERATE
	C	No data available for this stratum				
	D	RV5 versus placebo: Based on data from 5336 participants in 4 randomised controlled trials	1431 per 100,000	1572 per 100,000 Difference: 141 fewer per 100,000 people vaccinated (645 fewer to 629 more) Relative risk (95% CI): 0.91 (0.59 to 1.4)	No difference	⊕⊕⊕⊕ HIGH
	E	RV1 versus placebo: Based on data from 1494 participants in 3 randomised controlled trials	3654 per 100,000	3887 per 100,000 Difference: 233 fewer per 100,000 people vaccinated (0 to 428 fewer) Relative risk (95% CI): 0.94 (0.89 to 1)	No difference	⊕⊕⊕O MODERATE
Serious adverse events (1 month – 2 years follow up)	D	Rotasiil versus placebo: Based on data from 11,651 participants in 2 randomised	14,018 per 100,000	14,756 per 100,000 Difference: 738 fewer per 100,000 people vaccinated (1918 fewer to 443 more)	No difference	⊕⊕⊕⊕ HIGH

		controlled trials	Relative risk (95% CI): 0.95 (0.87 to 1.03)		
Serious adverse events (1 month – 2 years follow up)	D	Rotavac versus placebo: Based on data from 8210 participants in 3 randomised controlled trials	18,939 per 100,000	20,365 per 100,000 Difference: 1426 fewer per 100,000 people vaccinated (3055 fewer to 407 more) Relative risk (95% CI): 0.93 (0.85 to 1.02)	No difference	⊕⊕⊕⊕ HIGH
Intussusception (up to 3 years follow-up)		RV1 versus placebo: Based on data from 106,973 participants in 21 randomised controlled trials	60 per 100,000	86 per 100,000 Difference: 26 fewer per 100,000 people vaccinated (47 fewer to 4 more) Odds ratio (95% CI): 0.7 (0.46 to 1.05)	No difference	⊕⊕⊕O MODERATE
Intussusception (up to 2 years follow-up)		RV5 versus placebo: Based on data from 85,495 participants in 16 randomised controlled trials	36 per 100,000	48 per 100,000 Difference: 12 fewer per 100,000 people vaccinated (30 fewer to 20 more) Odds ratio (95% CI): 0.74 (0.38 to 1.42)	No difference	⊕⊕⊕O MODERATE
Intussusception (up to 2 years follow-up)		Rotasiil versus placebo: Based on data from 11,591 participants in 2 randomised controlled trials	69 per 100,000	52 per 100,000 Difference: 17 more per 100,000 people vaccinated (36 fewer to 256 more) Odds ratio (95% CI): 1.33 (0.3 to 5.97)	No difference	⊕⊕OO LOW
Intussusception (up to 2 years follow-up)		Rotavac versus placebo: Based on data from 8582 participants in 4 randomised controlled trials	141 per 100,000	106 per 100,000 Difference: 35 more per 100,000 people vaccinated (69 fewer to 428 more) Odds ratio (95% CI): 1.33 (0.35 to 5.04)	No difference	⊕⊕OO LOW

*Systematic review of serious adverse events associated with RV vaccination - http://www.who.int/vaccine_safety/publications/WHO_Rotavirus_vaccines_systematic_review_Cochrane.pdf.

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