JAMA Pediatrics | Original Investigation

Association of Rotavirus Vaccines With Reduction in Rotavirus Gastroenteritis in Children Younger Than 5 Years

A Systematic Review and Meta-analysis of Randomized Clinical Trials and Observational Studies

Zi-Wei Sun, MSc; Yu Fu, BS; Hai-Ling Lu, MD; Rui-Xia Yang, MD; Hemant Goyal, MD; Ye Jiang, MSc; Hua-Guo Xu, MD, PhD

IMPORTANCE Rotavirus vaccines have been introduced worldwide, and the clinical association of different rotavirus vaccines with reduction in rotavirus gastroenteritis (RVGE) after introduction are noteworthy.

OBJECTIVE To evaluate the comparative benefit, risk, and immunogenicity of different rotavirus vaccines by synthesizing randomized clinical trials (RCTs) and observational studies.

DATA SOURCES Relevant studies published in 4 databases: Embase, PubMed, the Cochrane Library, and Web of Science were searched until July 1, 2020, using search terms including "rotavirus" and "vaccin*."

STUDY SELECTION Randomized clinical trials and cohort and case-control studies involving more than 100 children younger than 5 years that reported the effectiveness, safety, or immunogenicity of rotavirus vaccines were included.

DATA EXTRACTION AND SYNTHESIS A random-effects model was used to calculate relative risks (RRs), odds ratios (ORs), risk differences, and 95% CIs. Adjusted indirect treatment comparison was performed to assess the differences in the protection of Rotarix and RotaTeq.

MAIN OUTCOMES AND MEASURES The primary outcomes were RVGE, severe RVGE, and RVGE hospitalization. Safety-associated outcomes involved serious adverse events, intussusception, and mortality.

RESULTS A meta-analysis of 20 RCTs and 38 case-control studies revealed that Rotarix (RV1) significantly reduced RVGE (RR, 0.316 [95% CI, 0.224-0.345]) and RVGE hospitalization risk (OR, 0.347 [95% CI, 0.279-0.432]) among children fully vaccinated; RotaTeq (RV5) had similar outcomes (RVGE: RR, 0.350 [95% CI, 0.275-0.445]; RVGE hospitalization risk: OR, 0.272 [95% CI, 0.197-0.376]). Rotavirus vaccines also demonstrated higher protection against severe RVGE. Additionally, no significant differences in the protection of RV1 and RV5 against rotavirus disease were noted in adjusted indirect comparisons. Moderate associations were found between reduced RVGE risk and Rotavac (RR, 0.664 [95% CI, 0.548-0.804]), Rotasiil (RR, 0.705 [95% CI, 0.605-0.821]), and Lanzhou lamb rotavirus vaccine (RR, 0.407 [95% CI, 0.332-0.499]). All rotavirus vaccines demonstrated no risk of serious adverse events. A positive correlation was also found between immunogenicity and vaccine protection (eg, association of RVGE with RV1: coefficient, −1.599; adjusted R^2, 99.7%).

CONCLUSIONS AND RELEVANCE The high protection and low risk of serious adverse events for rotavirus vaccines in children who were fully vaccinated emphasized the importance of worldwide introduction of rotavirus vaccination. Similar protection provided by Rotarix and RotaTeq relieves the pressure of vaccines selection for health care authorities.

Supplemental content

Editorial

Author Affiliations: Department of Laboratory Medicine, the First Affiliated Hospital with Nanjing Medical University, Nanjing, Jiangsu, China (Sun, Yang, Jiang, Xu); Department of Pathology, the First Affiliated Hospital with Nanjing Medical University, Nanjing, Jiangsu, China (Fu); Department of Laboratory Medicine, Yancheng Traditional Chinese Medicine Hospital Affiliated to Nanjing University of Chinese Medicine, Yancheng, China (Lu); The Wright Center of Graduate Medical Education, Scranton, Pennsylvania (Goyal).

Corresponding Author: Hua-Guo Xu, MD, PhD, Department of Laboratory Medicine, the First Affiliated Hospital, Nanjing Medical University, 300 Guang Zhou Rd, Nanjing, Jiangsu Province 210029, China (huaguoxu@njmu.edu.cn).

JAMA Pediatr. 2021;175(7):e210347. doi:10.1001/jamapediatrics.2021.0347
Published online May 10, 2021.

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

Worldwide, diarrhea, accounting for approximately 70.6 deaths per 100 000 population and 1.75 episodes per child in 2016, is the fifth leading cause of death among children younger than 5 years.[1] Rotavirus gastroenteritis, which results in 28.8% of the deaths from diarrhea, is the leading causative mechanism for diarrhea in children younger than 5 years.[1,2] The mortality and morbidity of RVGE varies by location, with the highest in sub-Saharan Africa, Southeast Asia, and South Asia.[2] Fortunately, the mortality of RVGE decreased by 43.6% from 2005 to 2015,[3] which most likely owing to the introduction of rotavirus vaccines.

In 2018, 101 countries have introduced rotavirus vaccine into their national immunization programs, with global coverage at 53%.[4] At present, 6 oral rotavirus vaccines have been widely used. Two live attenuated oral rotavirus vaccines, Rotarix (RV1), a 2-dose monovalent (G1P[8]) vaccine and RotaTeq [RV5]), a 3-dose pentavalent (G1, G2, G3, G4, and P[8]) vaccine, are globally introduced.[5] Another 2 novel vaccines, Rotasiil (BRV-PV) and Rotavac (116E), are currently licensed in India only.[6] Besides, domestically licensed rotavirus vaccines are also available in China (Lanzhou lamb rotavirus [LLR] vaccine) and Vietnam (Rotavin). Although a decline in the morbidity and mortality of RVGE has been reported in many countries following the introduction of rotavirus vaccines, concerns about serious adverse events still exist. Furthermore, little is known about the comparative benefit and risk of different rotavirus vaccines because of the lack of powerful head-to-head comparisons. Therefore, by synthesizing randomized clinical trials (RCTs) and case-control and cohort studies, we undertook a systematic review and meta-analysis to evaluate the association of different rotavirus vaccines with RVGE in aspects of benefit, risk, and immunogenicity and analyzed comparative protection of different vaccines by indirect comparisons.

Key Points

Question Is there a strong association of rotavirus vaccines and preventing rotavirus gastroenteritis (RVGE)?

Findings Meta-analysis revealed that Rotarix and RotaTeq reduced RVGE in children younger than 5 years by 68.4% and 63.6%, respectively, and this was confirmed in case-control studies (65.3% and 72.8%, respectively). Adjusted indirect comparisons indicated no significant differences in the protection of Rotarix and RotaTeq; other rotavirus vaccines, including Rotavac, Rotasiil, and Lanzhou lamb rotavirus vaccine, also showed positive associations with reduced RVGE risk.

Meaning The findings favor the worldwide introduction of rotavirus vaccines to prevent RVGE, but head-to-head comparisons are needed to compare the benefit and risk of different rotavirus vaccines.

Methods

Search Strategy and Selection Criteria

We searched for relevant studies published until July 1, 2018, and further updated until July 1, 2020, in 4 databases: Embase, PubMed, the Cochrane Library, and Web of Science, using search terms including "rotavirus" and "vaccin*." Randomized clinical trials and cohort and case-control studies reporting the efficacy, effectiveness, safety, or immunogenicity of rotavirus vaccine were included. Studies with fewer than 100 enrolled participants were excluded. The selection criteria are further outlined in detail in eTable 1 in the Supplement.

Procedures

The study selection and data collection process were explained in detail in the eMethods in the Supplement. Using EndNote X8 (Clarivate), 2 reviewers (Z.-W.S. and Y.F.) independently screened all obtained articles for relevance, with a third reviewer (H.L.L.) consulted when necessary. We developed a standardized data extraction form, and Z.-W.S. rechecked the extracted data of included trials identified by Y.F. The quality of RCTs and observational studies were accessed in accordance with the Cochrane Reviewers' Handbook and the Newcastle-Ottawa Scales (eTable 2 in the Supplement). For 10% of included studies, data were doubly extracted by a third author (H.L.L.). The procedure was supervised and arbitrated by a fourth author (H.G.X.).

Statistical Analysis

In preliminary analyses, estimates of relative risks (RRs), odds ratios (ORs), and risk differences using raw data were similar to reported results; thus, we opted to perform more detailed statistical analyses with raw data, using Stata version 12.0 (StataCorp) and Revman version 5.3 (Cochrane Library). The RRs, ORs, and risk differences were calculated in a Mantel-Haenszel random-effects model. We used the per-protocol estimates in RCTs and combined control groups, including both hospital and community controls, in case-control studies. Considering the diminished vaccine efficacy in low-income countries (LICs) compared with middle-income countries and high-income countries, included studies were stratified by the economic development of countries, using the World Bank's classification (eTable 3 in the Supplement).[7] For multicenter RCTs, we included each individual country as a separate observation point whenever possible. If not, we used the sample size in each site to calculate a weighted level of economic development and used this estimate to assign the trial to a specific stratum.

Adjusted indirect treatment comparison was performed to assess the differences in vaccine protection between different subgroups, adopting $P < .05$ as the level of statistical significance. We performed a metaregression model to estimate the association between vaccine protection in 1 to 2 years of follow-up and the rate of seropositivity at 1 to 2 months after the last dose (IgA antibody concentration ≥20 units/mL or ≥3-fold increase from baseline), and the adjusted R^2 index was used to quantify the proportion of variance explained by the covariates. For the outcomes obtained from fewer than 3 studies, we conducted a systematic review. A sensitivity analysis was performed by excluding each study to identify the stability and consistency of our results. The Q test and I^2 statistic

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

was applied to determine heterogeneity ($P < .10$ or $I^2 > 50\%$ indicated significant heterogeneity). Publication bias was assessed using funnel plots (eFigure 6 in the Supplement).

Results

Study Selection and Characteristics

Initial literature retrieval produced 3998 articles, and 241 full-text articles were assessed for eligibility. Seventeen studies were further identified from updated literature retrieval, and 121 studies were finally included. The selection process is summarized in eFigure 1 in the Supplement. Included studies varied by study design (57 RCTs,[8-64] 50 case-control studies,[65-114] and 14 cohort studies[115-128]), rotavirus vaccine type (74 for RV1[8,9,11,12,15,16,19-26,31,32,34,35,40-44,48-52,58,65,66,72-85,87,88,96-110,113,114,118-122,124-128]; 45 for RV5[10,13,14,17,18,27-29,33,45,53-57,59-71,76,78,81,84,86,88,93-96,111,112,115-117,122,123]; 5 for LLR[30,89-92]; and 3 each for Rotavac[36-38] and Rotasiil[39,46,47]), or study population. The characteristics of included studies are reported in eTable 4 in the Supplement.

Benefits and Risks of Rotavirus Vaccines, Stratified by Vaccine Type

During the first year of follow-up, more children in placebo groups developed RVGE compared with children vaccinated with full-dose RV1 (RR, 0.316 [95% CI, 0.224-0.345]) or RV5 (RR, 0.350 [95% CI, 0.275-0.445]) (**Figure 1** and **Figure 2**). In case-control studies, a low risk of RVGE hospitalization was also estimated among children fully vaccinated with RV1 (OR, 0.347 [95% CI, 0.279-0.432]) or RV5 (OR, 0.272 [95% CI, 0.197-0.376]). A systemic review of cohort studies revealed RRs of 0.125 (95% CI, 0.086-0.182) for RV1 and 0.049 (95% CI, 0.028-0.083) for RV5 for the prevention of RVGE hospitalization, regardless of the cohort year (eTable 5 in the Supplement). Rotavirus vaccines demonstrated higher protection against severe RVGE but less against severe all-cause gastroenteritis. A clear gradient in vaccine protection was noted by country income level, with the highest in high-income countries and the lowest in LICs (RVGE hospitalization, $P = .002$; RVGE, $P < .001$; eTables 6-12 in the Supplement).

Rotavac reduced RVGE and severe RVGE risk in India by 33.6% (95% CI, 19.6%-45.2%) and 56.0% (95% CI, 37.3%-69.2%), respectively. Rotasiil reduced RVGE and severe RVGE risk by 29.5% (95% CI, 17.9%-39.5%) and 52.2% (95% CI, 12.1%-74.0%) in India and Niger, respectively. In China, LLR was associated with a decrease in RVGE (RR, 0.407 [95% CI, 0.332-0.499]; OR, 0.348 [95% CI, 0.121-0.999]), severe RVGE (RR, 0.248 [95% CI, 0.144-0.427]), and RVGE hospitalization (OR, 0.405 [95% CI, 0.309-0.531]).

In indirect treatment comparisons, no significant differences were noted in the protection of RV1 and RV5 against RVGE (RR, 0.865 [95% CI, 0.565-1.325]; $P = .51$; OR, 1.264 [95% CI, 0.866-1.844]; $P = .23$) or severe RVGE (RR, 0.768 [95% CI, 0.335-1.758]; $P = .53$; OR, 0.944 [95% CI, 0.603-1.476]; $P = .80$) (eTable 13 in the Supplement). When stratified by the World Bank classification, there were also no significant differences in vaccine protection between RV1 and RV5. Furthermore, to alleviate the bias of sociodemographic factors, only studies conducted in the same region were included to perform adjusted indirect treatment comparison, and the results also indicated little difference in vaccine protection between RV1 and RV5 (eTable 14 in the Supplement).

We identified 36 RCTs,[9,11-14,16-20,23,24,26,27,29,30,32-35,37-43,45,47,48,50,53,58,60,61,63] 4 case-control studies,[71,81,101,107] and 2 cohort studies[117,119] evaluating the safety of rotavirus vaccines (eFigures 2-4 in the Supplement). The incidence of serious adverse events in the vaccine group was similar to that of the placebo group. The overall estimate of risk differences showed no increased risk of intussusception and death in children vaccinated with RV1, RV5, Rotavac, Rotasiil, or LLR during 1 or 2 years of follow-up.

Stratified Analyses of Rotavirus Vaccine Benefit by Duration and Vaccination Schedule

In stratified analyses of the duration of vaccine protection, we found that the protection of RV1 or RV5 against RVGE was lower in the second year of follow-up (RV1: RR, 0.494 [95% CI, 0.255-0.955]; RV5: RR, 0.622 [95% CI, 0.388-0.996]) in comparisons with the first year of follow-up (RV1: RR, 0.297 [95% CI, 0.207-0.425]; RV5: RR, 0.344 [95% CI, 0.271-0.436]), while similar in 2 years of follow-up (RV1: RR, 0.348 [95% CI, 0.196-0.618]; RV5: RR, 0.500 [95% CI, 0.288-0.869]; **Figure 3**). Also, the reductions in vaccine protection during the second year of follow-up were small in the high-income countries (RV1: RR, 0.281 [95% CI, 0.207-0.381]; RV5: RR, 0.497 [95% CI, 0.353-0.699]) but pronounced in the LICs (RV1: RR, 1.288 [95% CI, 0.738-2.248]; RV5: RR, 0.815 [95% CI, 0.659-1.007]) (eTable 9 in the Supplement). Here, estimates should be interpreted with caution, because there was only 1 study for an LIC.[48] Similar results were observed for Rotavac and Rotasiil in India. In case-control studies, RV1 and RV5 provided similar protection among children aged younger than 12 months, 12-24 months, or ≥12 months. By contrast, the OR of RV1 vs control in the LIC and lower- and middle-income countries was significantly lower among children aged 12 to 24 months (OR, 0.528 [95% CI, 0.249-1.120]; $P < .001$) or those 12 months or older (OR, 0.526 [95% CI, 0.370-0.750]; $P = .008$), compared with children younger than 12 months (OR, 0.356 [95% CI, 0.266-0.476]).

In the second comparison, we divided 35 case-control studies[65-74,79,80,85-88,93-96,98-100,102-106,108-114] depending on whether the enrolled children received complete vaccination (Figure 3). Studies reported a nonsignificantly lower risk of RVGE hospitalization among children vaccinated with 3-dose RV5 compared with 1 dose, but a similar risk between 2 doses and 3 doses. When stratified by the World Bank classification, no significant differences in vaccine protection between 3 doses, 2 doses, and 1 dose of RV5 were observed. Two-dose RV1 showed stronger association with reduced risk of RVGE hospitalization than only 1 dose (OR, 0.347 [95% CIs, 0.279-0.432] vs 0.561 [95% CIs, 0.493-0.639]; $P < .001$), especially in the middle-income countries (OR, 0.396 [95% CIs, 0.338-0.465] vs 0.559 [95% CIs, 0.489-0.640]; $P = .001$).

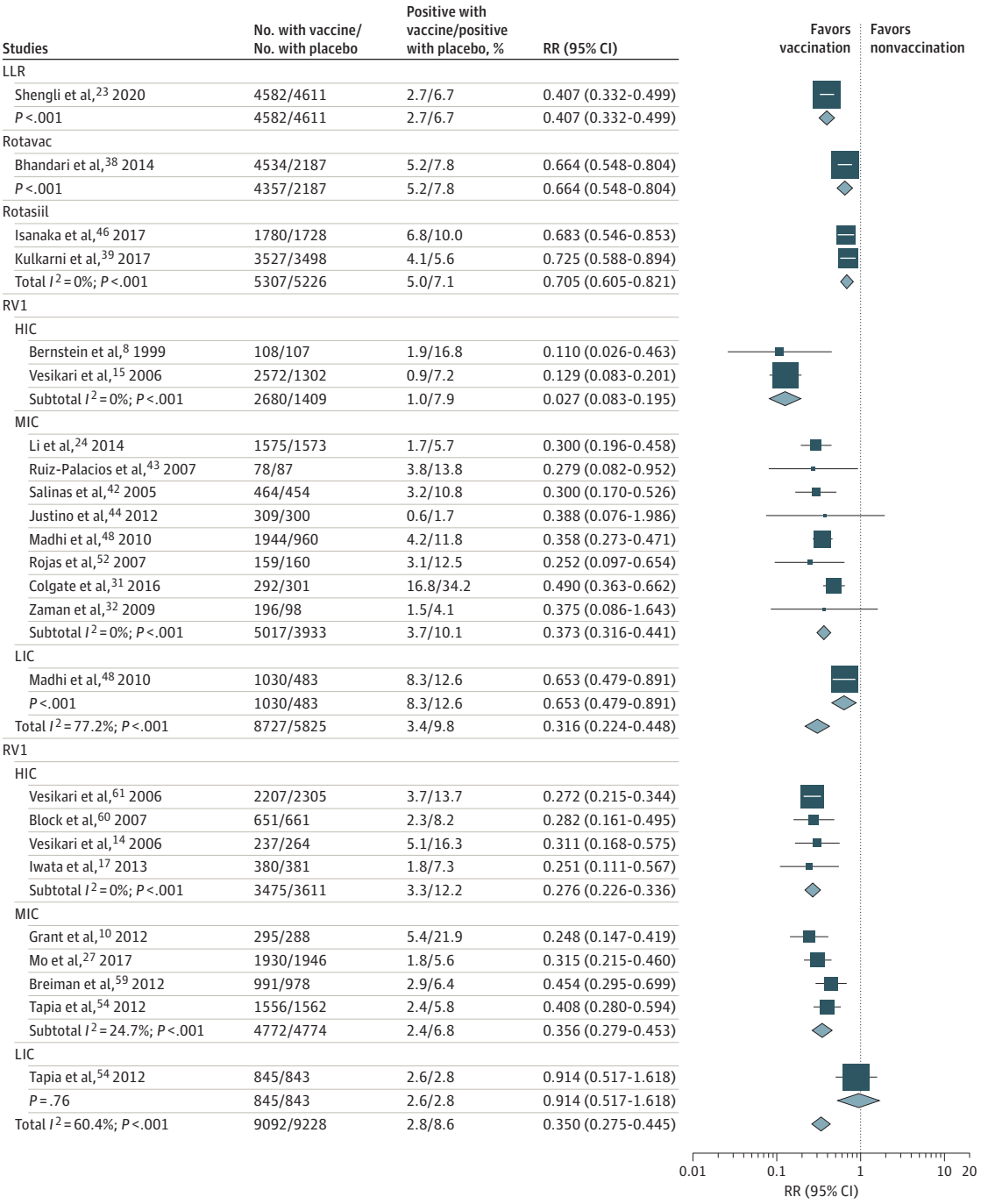
Strain-Specific Protection of Rotavirus Vaccine

Pooled data from 13 RCTs[11,16,20,24,27,40-42,48,49,54,59,61] suggested that RV1 conferred protection against severe RVGE

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

Figure 1. Random-Effects Model of Rotavirus Vaccine Protection Against Rotavirus Gastroenteritis (RVGE) and RVGE Hospitalization, by Country Income Level, in Randomized Clinical Trials



HIC indicates high-income countries; LIC, low-income countries; LLR, Lanzhou lamb rotavirus; MIC, middle-income countries; RR, relative risk; RV1, monovalent rotavirus vaccine.

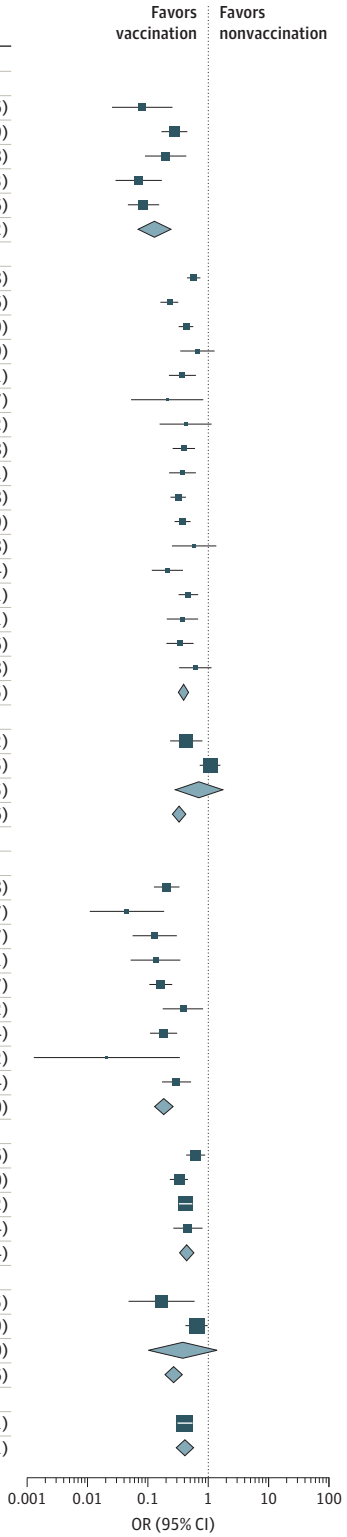
caused by G1, G2, G3, G4, G9, and P[8] strains, respectively, whereas the protection of RV5 was low (and nonsignificant) against G1, G2, and G3 strain (eTable 15 in the Supplement). The **Table** showed the strain-specific protection of RV1,[129] and no significant differences were noted in vaccine protection against partly heterotypic or fully heterotypic strains compared with homotypic strains in middle-income countries. There were also no significant differences in vaccine protection against single-antigen vaccine type and single-antigen nonvaccine type strains for RV1 and RV5. However, higher protection of RV1 against homotypic strains (OR, 0.116 [95% CIs, 0.065-0.217]) than heterotypic strains (OR, 0.457, [95% CIs,

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

Figure 2. Random-Effects Model of Rotavirus Vaccine Protection against Rotavirus Gastroenteritis (RVGE) and RVGE Hospitalization, by Country Income Level, in Case-Control Studies

Studies	No. with cases/ No. in control group	Vaccinations in cases/vaccinations in controls, %	OR (95% CI)
RV1			
HIC			
Chang et al,[88] 2014	184/1623	1.6/16.9	0.081 (0.026-0.256)
Cortese et al,[65] 2014	95/1442	23.2/51.7	0.282 (0.173-0.459)
Immergluck et al,[66] 2016	51/69	31.4/69.6	0.200 (0.091-0.438)
Doll et al,[72] 2015	31/316	22.6/80.4	0.071 (0.029-0.173)
Braeckman et al,[74] 2012	145/182	45.5/90.7	0.086 (0.047-0.156)
Subtotal I^2 = 71.7%; P < .001	506/3632	22.5/40.9	0.131 (0.071-0.242)
MIC			
Groome et al,[106] 2014	414/1100	67.1/77.8	0.583 (0.454-0.748)
Ichihara et al,[99] 2014	182/1682	63.2/88.0	0.233 (0.167-0.326)
Justino et al,[100] 2011	436/690	66.3/81.7	0.439 (0.333-0.579)
Cotes-Cantillo et al,[103] 2014	156/711	91.7/94.2	0.673 (0.352-1.289)
Mokomane et al,[109] 2017	205/317	79.0/90.9	0.379 (0.228-0.631)
Snelling et al,[80] 2009	14/57	21.4/56.1	0.213 (0.054-0.847)
Beres et al,[104] 2016	17/270	47.1/67.4	0.430 (0.160-1.152)
Gastañaduy et al,[96] 2016	125/483	32.8/54.9	0.402 (0.265-0.608)
Gastañaduy et al,[108] 2016	205/317	79.0/90.9	0.379 (0.228-0.631)
Patel et al,[98] 2013	300/1561	69.3/87.6	0.321 (0.241-0.428)
de Palma et al,[73] 2010	251/770	60.6/80.1	0.381 (0.280-0.519)
Armah et al,[110] 2016	206/439	95.1/97.0	0.598 (0.258-1.388)
Gheorghita et al,[79] 2016	89/745	15.7/46.7	0.213 (0.118-0.384)
Pringle et al,[102] 2016	294/362	69.0/82.3	0.479 (0.332-0.691)
Lopez et al,[85] 2018	107/202	72.9/87.6	0.380 (0.209-0.691)
Khagayi et al,[114] 2019	84/377	60.7/81.7	0.346 (0.208-0.576)
Eraliev et al,[87] 2020	92/452	82.6/88.5	0.618 (0.335-1.138)
Subtotal I^2 = 52.1%; P < .001	3117/10 535	68.6/81.3	0.396 (0.338-0.465)
LIC			
Bar-Zeev et al,[105] 2015	97/565	83.5/92.0	0.438 (0.236-0.812)
Mujuru et al,[113] 2018	888/2640	96.1/95.7	1.090 (0.740-1.605)
Subtotal I^2 = 83.5%; P = .46	985/3205	94.8/95.1	0.714 (0.292-1.745)
Total I^2 = 80.8%; P < .001	4492/16 543	69.0/74.9	0.338 (0.268-0.426)
RV5			
HIC			
Tate et al,[68] 2013	127/700	17.3/50.1	0.208 (0.129-0.338)
Donauer et al,[69] 2013	68/927	2.9/40.0	0.045 (0.011-0.187)
Cortese et al,[65] 2013	79/748	7.6/38.4	0.132 (0.057-0.307)
Boom et al,[70] 2010	72/214	6.9/35.5	0.136 (0.052-0.351)
Cortese et al,[71] 2011	283/2861	8.1/34.6	0.167 (0.108-0.257)
Immergluck et al,[66] 2016	57/55	38.6/61.8	0.388 (0.181-0.832)
Staat et al,[67] 2011	167/745	10.2/37.9	0.186 (0.110-0.314)
Chang et al,[88] 2014	184/1520	0.0/11.3	0.021 (0.001-0.342)
Muhsen et al,[86] 2018	72/425	63.9/85.4	0.302 (0.174-0.524)
Subtotal I^2 = 49.2%; P < .001	1109/8195	12.9/35.7	0.186 (0.133-0.260)
MIC			
Patel et al,[93] 2009	209/1044	75.6/83.1	0.628 (0.441-0.896)
Mast et al,[94] 2011	357/1550	82.1/93.2	0.336 (0.240-0.470)
Patel et al,[95] 2012	849/7309	91.0/95.9	0.432 (0.332-0.562)
Gastañaduy et al,[96] 2016	103/323	18.4/32.5	0.470 (0.271-0.814)
Subtotal I^2 = 53.4%; P < .001	1518/10 226	81.9/92.2	0.450 (0.347-0.584)
LIC			
Tate et al,[112] 2016	29/90	10.3/40.0	0.173 (0.049-0.615)
Bonkoungou et al,[111] 2017	172/582	77.3/83.8	0.657 (0.432-0.999)
Subtotal I^2 = 80.8%; P < .001	201/672	67.7/77.0	0.386 (0.106-1.410)
Total I^2 = 80.8%; P < .001	2828/19 093	53.8/67.5	0.272 (0.197-0.376)
LLR			
Fua et al,[89] 2007	838/838	10.7/22.9	0.405 (0.309-0.531)
Subtotal I^2 = 49.2%; P < .001	838/838	10.7/22.9	0.405 (0.309-0.531)



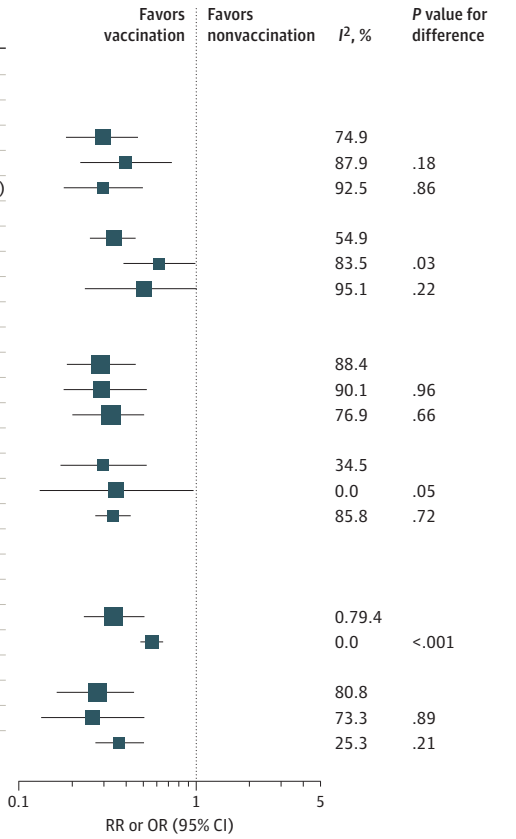
HIC indicates high-income countries; LIC, low-income countries; LLR, Lanzhou lamb rotavirus; MIC, middle-income countries; OR, odds ratio; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine.

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

Figure 3. Subgroup Analysis for Rotavirus Vaccine Protection, Stratified by Follow-up Duration and Vaccination Schedule

	No. of studies	No. vaccinated/ Total No.	No. affected/ Total No.	RR or OR (95% CI)	I^2, %	*P* value for difference
Follow-up duration						
RCT						
RV1						
First year	10	297/8727	569/5825	0.297 (0.207-0.425)	74.9	
Second year	4	139/4776	231/3453	0.494 (0.255-0.955)	87.9	.18
Two years	5	251/5479	516/3908	0.348 (0.1.96-0.618)	92.5	.86
RV5						
First year	7	238/8797	727/8940	0.344 (0.271-0.436)	54.9	
Second year	3	219/3884	324/3786	0.622 (0.388-0.996)	83.5	.03
Two years	3	389/5555	806/5631	0.500 (0.288-0.869)	95.1	.22
Case-control studies						
RV1						
<12 mo old	13	1584/2534	8024/9667	0.312 (0.211-0.461)	88.4	
12-24 mo old	8	526/1353	4310/6420	0.317 (0.192-0.522)	90.1	.96
≥12 mo old	10	2672/4107	22 506/26 630	0.352 (0.245-0.504)	76.9	.66
RV5						
<12 mo old	6	81/219	879/2164	0.299 (0.171-0.523)	34.5	
12-24 mo old	5	73/502	1228/2473	0.156 (0.114-0.215)	0.0	.05
≥12 mo old	3	126/662	597/1538	0.356 (0.164-0.771)	85.8	.72
Vaccination schedule						
Case-control studies						
RV1						
2 doses	24	3227/4668	13 101/17 372	0.347 (0.279-0.432)	0.79.4	
1 dose	20	611/1803	1826/5124	0.561 (0.493-0.639)	0.0	<.001
RV5						
3 doses	15	1522/2828	12 879/19 093	0.272 (0.197-0.376)	80.8	
2 doses	9	96/835	1129/4752	0.260 (0.149-0.453)	73.3	.89
1 dose	8	84/750	705/2619	0.365 (0.264-0.504)	25.3	.21



In randomized clinical trials (RCTs), the first column shows the number of cases in the vaccine group and the total population in the vaccine group. In case-control studies, these numbers denote the number of vaccinated children in the case group and the sum of children with no vaccination plus those receiving full doses in the case group. In RCTs, the second column shows the number of cases in the placebo group and the total population in placebo group. In case-control studies, this column shows the number of vaccinated children in the control group and the sum of children with no vaccination plus those receiving full doses in the control group. Odds ratios (ORs) were used for case-control studies; relative risks (RRs), for RCTs. RV1 indicates monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine.

0.264-0.579]) was estimated in case-control studies in middle-income countries (P = .005).

Metaregression Between Immunogenicity and Protection of Rotavirus Vaccine

Circulating antirotavirus IgA antibodies have been used as the early proxy for vaccine uptake,[130,131] which is a convenient method to monitor vaccine effectiveness at the population level. Pooled data from 24 RCTs[8,9,12,14-16,18,19,22,24,28,29,31-35,42,43,48,53,57,60,61] showed that the percentage of seropositivity among children who were fully vaccinated was 69.3% (95% CIs, 60.0%-78.6%) for RV1 and 89.5% (95% CIs, 84.5%-94.5%) for RV5, much higher than in placebo group (11.9% [95% CIs, 8.5%-15.2%]). Moreover, the percentage of vaccinated children with seropositivity exhibited a positive association with vaccine protection (R^2 >0; (eg, association of RVGE with Rotarix: coefficient, −1.599; adjusted R^2, 99.7%; **Figure 4**). In metaregression analyses, with the difference of the rate of seropositivity between vaccine groups and placebo groups as the abscissa, the adjusted R^2 values for the associations between immunogenicity and vaccine protection were 86.5% for RV1 and 15.6% for RV5 against severe RVGE and 99.7% for RV1 against RVGE. We did not evaluate the association between immunogenicity and vaccine protection of RV5 against RVGE because only 3 studies[15,60,61] were included.

Sensitivity and Heterogeneity Analyses

Our systematic review found considerable heterogeneity between included studies. To investigate the potential sources of heterogeneity, a subgroup analysis was performed using economic development as a variable, and the heterogeneity was subsequently shown to be dealt with in varying degrees when I^2 was greater than 50%. Sensitivity analyses for all outcomes did not identify any substantial effects resulting from differences in study quality (eFigure 5 in the Supplement).

Discussion

Our findings from RCTs, case-control studies, and cohort studies corroborated that RV1 and RV5 have substantial and sustained protection against rotavirus disease, especially against

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

Table. Strain-Stratified Vaccine Protection During the 2-Year Efficacy Period

Characteristic	RV1			RV5		
	Observations, No.	RR or OR (95% CI)[a]	*P* value[b]	Observations, No.	RR or OR (95% CI)[a]	*P* value[b]
RCTs[c]						
High-income countries						
Single-antigen vaccine type strain	4	0.054 (0.022-0.130)	NA	4	0.056 (0.036-0.088)	NA
Single-antigen nonvaccine type strain	9	0.123 (0.076-0.198)	.11	2	0.098 (0.010-0.945)	.63
Middle-income countries						
Homotypic strain	3	0.248 (0.139-0.444)	NA	NA	NA	NA
Partly heterotypic strain	7	0.200 (0.131-0.306)	.56	NA	NA	NA
Fully heterotypic strain	3	0.333 (0.191-0.581)	.47	NA	NA	NA
Single-antigen vaccine type strain	4	0.293 (0.196-0.438)	NA	13	0.533 (0.423-0.672)	NA
Single-antigen nonvaccine type strain	10	0.204 (0.151-0.276)	.16	8	0.443 (0.285-0.690)	.47
Low-income countries						
Single-antigen vaccine type strain	2	0.558 (0.315-0.991)	NA	NA	NA	NA
Single-antigen nonvaccine type strain	6	0.485 (0.336-0.701)	.69	NA	NA	NA
Case-control studies[d]						
High-income countries						
Homotypic strain	3	0.096 (0.030-0.313)	NA	2	0.156 (0.091-0.268)	NA
Partly heterotypic strain	3	0.188 (0.063-0.555)	.41	3	0.135 (0.041-0.445)	.83
Fully heterotypic strain	3	0.178 (0.107-0.295)	.35	NA	NA	NA
Single-antigen vaccine type strain	NA	NA	NA	3	0.165 (0.101-0.271)	NA
Single-antigen nonvaccine type strain	NA	NA	NA	2	0.215 (0.105-0.441)	.56
Middle-income countries						
Homotypic strain	2	0.116 (0.065-0.217)	NA	NA	NA	NA
Partly heterotypic strain	4	0.457 (0.264-0.579)	.001	NA	NA	NA
Fully heterotypic strain	6	0.335 (0.197-0.569)	.005	NA	NA	NA
Single-antigen vaccine type strain	2	0.458 (0.147-1.427)	NA	5	0.354 (0.249-0.503)	NA
Single-antigen nonvaccine type strain	4	0.592 (0.310-1.129)	.70	3	0.176 (0.039-0.793)	.38
Low-income countries						
Single-antigen vaccine type strain	1	0.201 (0.065-0.617)	NA	NA	NA	NA
Single-antigen nonvaccine type strain	2	0.516 (0.232-1.147)	.21	NA	NA	NA
Cohort studies[e]						
Middle-income countries						
Homotypic strain	2	0.276 (0.096-0.794)	NA	NA	NA	NA
Partly heterotypic strain	3	0.436 (0.183-1.039)	.25	NA	NA	NA
Fully heterotypic strain	4	0.429 (0.185-0.996)	.26	NA	NA	NA

Abbreviations: NA, not applicable; OR, odds ratio; RCTs, randomized clinical trials; RR, relative risk; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine; RVGE, rotavirus gastroenteritis.

[a] Relative risks are used in the RCT portion of this Table, and ORs are used in the case-control studies portion.

[b] *P* values were the differences of vaccine protection against partly heterotypic or fully heterotypic strains compared with homotypic strains; the differences of vaccine protection against single-antigen nonvaccine type strains compared with single-antigen vaccine type strains.

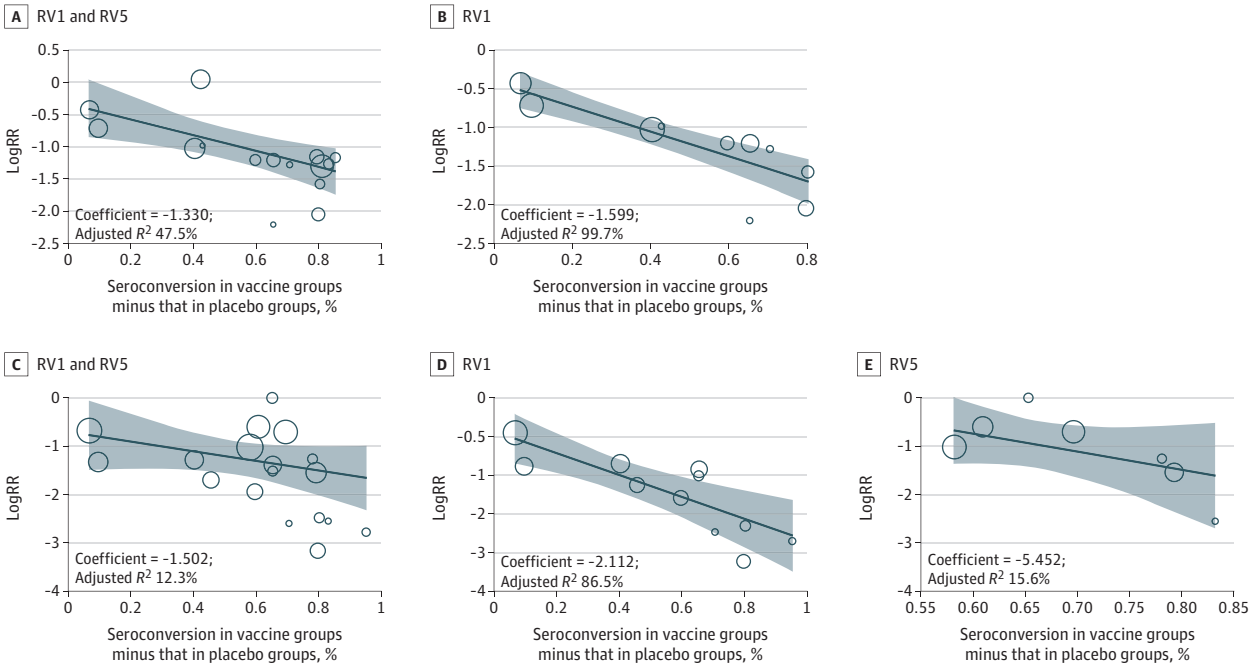
severe RVGE, which is in line with previously reported data.[132-135] Considering that vaccine administrations are not always followed by recommendations, comorbidities may be present, and sociodemographic factors vary in real world, the consistency of results from observational studies and RCTs reconfirmed the high protection of rotavirus vaccination. Moreover, pooled data showed no increased risk of serious adverse events including intussusception among children who were vaccinated.[136,137] However, a study about intussusception conducted in Australia reported a smaller increased risk of intussusception after RV1 and RV5 vaccination.[138] Therefore, continuous surveillance of the benefits and adverse effects of rotavirus vaccines is required after vaccination.

The protection against rotavirus diseases varied by time interval after vaccination, and rotavirus vaccines, particularly RV5, provided lower protection against RVGE in the second efficacy period. Although our results indicated that rotavirus vaccines can provide substantial protection against RVGE during the first 2 years of life,[139] more studies following up the vaccine efficacy for more than 2 years are required. The reduced vaccine protection might be caused by declining vaccine-induced antibodies, acquisition of protection against RVGE through indirect effects of vaccine, or exposure to natural asymptomatic and mild infections among control populations who are unvaccinated.[140] The wane of vaccine protection over time highlights the importance of monitoring the mor-

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

Figure 4. Metaregression Between Immunogenicity and Vaccine Protection



The coefficient is the regression correlation coefficient, and the adjusted R^2 is the proportion of between-study variance explained. Metaregression between immunogenicity and logRR against rotavirus gastroenteritis (RVGE) for RV1 and RV5 (A), RVGE for RV1 (B), severe RVGE for RV1 and RV5 (C), severe RVGE for RV1 (D), and severe RVGE for RV5 (E). RV1 indicates monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine.

bidity of rotavirus diarrhea after vaccination; more children may become infected at older ages, and evaluation of alternative vaccination schedules is useful.

During the subgroup analyses, vaccination schedule may affect vaccine performance. Data from case-control studies identified that a partial vaccination provided considerable protection, but not to the same level as a full series.[133,141] Several phase 3 RCTs also showed that RV1 and RV5 conferred early protection against RVGE before completion of a 2-dose or 3-dose schedule.[11,142] This finding is encouraging so that numerous children who are partly vaccinated in LICs and children vaccinated during the periods of intensive rotavirus circulation can receive protection. Nonetheless, the protection of partial vaccination was lower than full vaccination, and the duration of protection from partial vaccination was not clear. Therefore, more efforts should be made to ensure full vaccination as recommended to achieve optimal protection.

The wide variety of rotavirus strain is a challenge for improving vaccine effectiveness. It is encouraging that RV1 and RV5 work well against heterotypic strains. The heterotypic protective immunity is important for low-income and lower middle-income countries, where greater strain diversity and concurrent circulation of several strains is a common phenomenon.[143] However, prevalent rotavirus strain varied by time and region, and the dominance of 1 strain was often followed by the replacement with other strains.[144] The changes of serotype distribution was also reported in some countries after vaccine introduction.[145-147] Therefore, the characterization of rotavirus strains after vaccination should be monitored to avoid population-based selection of so-called escape strains, especially fully heterotypic strains and new strains, because of the long-term pressure of vaccine immunity.[148]

A clear gradient in rotavirus vaccine protection was noted by country income level, with the highest in high-income countries.[11,33,48,53,149] Possible reasons for weaker vaccine protection in LICs include host characteristics, such as malnutrition[150]; environmental enteropathy[151]; concomitant enteric infections[152]; poor maternal health[151]; high titers of RV-specific maternal antibodies in breast milk[153,154]; and interference by coadministration of oral poliovirus vaccine.[155] Besides, most children in LICs were not vaccinated as per the recommended schedule and subsequently received lower protection from partial vaccination. The lower-than-expected rotavirus protection in LICs can also be explained by high natural rotavirus infections before vaccination, which confer protection against subsequent RVGE and may cause a biased outcome.[43,156,157] Furthermore, the scarcity of clean water can increase the risk of rotavirus spread by fecal-oral transmission in LICs. However, since the greater burden of severe RVGE in middle-income countries and LICs, the cases of severe RVGE prevented by rotavirus vaccines seem to be more in these settings. In addition, rotavirus vaccination was found to be cost-effective in LICs, suggesting a potential benefit of vaccination.[158,159]

Currently there are 6 rotavirus vaccines licensed in the market, but little was known about the interchangeability of these vaccines. Therefore, we performed adjusted indirect comparisons, which showed similar protection of RV1 and RV5,

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

Rotavac, and Rotasiil, particularly at the same economic level or in the same country. This relieves the pressure of vaccine selection and suggests that health care authorities should weigh not only vaccine effectiveness but also economic factors associated with vaccine procurement and introduction, such as unit price, cold-chain volume, the cost of storage, and wastage. Cost-effectiveness models in Kenya and Palestine have indicated that 2-dose RV1 vaccinations seems to be more cost-effective and create less strain on a cold chain than 3-dose RV5 vaccinations.[160,161] Additionally, the duration of high vaccine protection and the reduced vaccine protection resulted from partial vaccination should be taken into account. Furthermore, herd effects induced by rotavirus vaccination should be estimated to further compare the social benefits of different vaccines for children who are unvaccinated. It has been reported in Europe and the US that a herd effect of the rotavirus vaccine may enhance its clinical performance when implemented at a large scale under routine conditions.[162,163] Considering the inherent limitations of indirect comparisons, a well-designed head-to-head study should be conducted to further compare the efficacy, cost-effectiveness, and strain-specific protection of different vaccines.

Limitations

There are several limitations of our meta-analysis. First, despite a systematic search of published studies, the final estimates were identified in only 45 settings, and an exhaustive review of gray literature was not included. Especially in stratified analyses, sparse data in some subgroups limit generalizability; for example, there was only 1 available study conducted in an LIC. But the number of children enrolled in our meta-analysis was more than 100 000, suggesting the value and reliability of our results. Second, considering that the introduction and protection of rotavirus vaccines vary by regions, it may prevent a fair comparison of RV1 and RV5 at a global level. So, we also performed indirect comparisons in the same region. The most accurate method, head-to-head comparisons, to evaluate the comparative efficacy of different vaccines is required in further studies. Third, the missing data and low quality in some included studies may influence our results, although we have excluded studies with small enrolled populations (<100 children). Well-designed observational trials and RCTs are still required to evaluate the clinical performance of rotavirus vaccines.

Conclusions

In conclusion, based on a large worldwide data set, we identified reasonable evidence of sustained high protection and low risk of adverse effects for rotavirus vaccines in children aged 2 years or younger, which is important to combat vaccine hesitancy. Also, the differences in vaccine performance between 4 licensed rotavirus vaccines were not surprising. Although the global introduction of rotavirus vaccines faces many scientific, programmatic, and financial challenges, these licensed vaccines hold promise to have immediate and measurable effectiveness to improve child health and survival from rotavirus disease. Our findings and prelicensing evidence reinforce the importance of optimizing uptake rates of rotavirus vaccines worldwide. Continued surveillance after vaccine introduction is also required to monitor the long-term changes in rotavirus incidence and the potential emergence of heterotypic strains.

ARTICLE INFORMATION

Accepted for Publication: May 10, 2021.

Published Online: May 10, 2021. doi:10.1001/jamapediatrics.2021.0347

Author Contributions: Dr Xu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ms Sun and Mr Fu contributed equally to this work.
Concept and design: Fu, Lu, Yang, Goyal, Jiang, Xu.
Acquisition, analysis, or interpretation of data: Sun, Fu, Lu, Xu.
Drafting of the manuscript: Sun, Fu, Lu.
Critical revision of the manuscript for important intellectual content: Fu, Lu, Yang, Goyal, Jiang, Xu.
Statistical analysis: Sun, Fu, Lu.
Obtained funding: Xu.
Administrative, technical, or material support: Yang, Xu.
Supervision: Jiang, Xu.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was supported by the National Natural Science Foundation of China (grant 81302531), Natural Science Foundation of Jiangsu Province of China (grant BK20181492), the National Key Clinical Department of Laboratory Medicine of China in Nanjing, Key laboratory for Laboratory Medicine of Jiangsu Province (grant ZDXKB2016005), and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. GBD 2016 Diarrhoeal Disease Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis*. 2018;18(11):1211-1228. doi:10.1016/S1473-3099(18)30362-1

2. Troeger C, Khalil IA, Rao PC, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. *JAMA Pediatr*. 2018;172(10):958-965. doi:10.1001/jamapediatrics.2018.1960

3. Collaborators GDD; GBD Diarrhoeal Diseases Collaborators. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis*. 2017;17(9):909-948. doi:10.1016/S1473-3099(17)30276-1

4. Peck M, Gacic-Dobo M, Diallo MS, Nedelec Y, Sodha SV, Wallace AS. Global routine vaccination coverage, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(42):937-942. Correction published in *MMWR Morb Mortal Wkly Rep*. 2019;68(44):1010. doi:10.15585/mmwr.mm6842a1

5. World Health Organization. Rotavirus vaccines: WHO position paper, January 2013. *Wkly Epidemiol Rec*. 2013;88(5):49-64.

6. World Health Organization. Immunization, vaccines and biologicals. Updated October 2020. Accessed February 26, 2019. https://www.who.int/immunization/diseases/rotavirus/en/

7. Collaborators GM; GBD 2016 Mortality Collaborators. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1084-1150. doi:10.1016/S0140-6736(17)31833-0

8. Bernstein DI, Sack DA, Rothstein E, et al. Efficacy of live, attenuated, human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial. *Lancet*. 1999;354(9175):287-290. doi:10.1016/S0140-6736(98)12106-2

9. Dennehy PH, Brady RC, Halperin SA, et al; North American Human Rotavirus Vaccine Study Group. Comparative evaluation of safety and immunogenicity of two dosages of an oral live attenuated human rotavirus vaccine. *Pediatr Infect*

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

Dis J. 2005;24(6):481-488. doi:10.1097/01.inf.0000164763.55558.71

10. Grant LR, Watt JP, Weatherholtz RC, et al. Efficacy of a pentavalent human-bovine reassortant rotavirus vaccine against rotavirus gastroenteritis among American Indian children. *Pediatr Infect Dis J*. 2012;31(2):184-188. doi:10.1097/INF.0b013e3182435afe

11. Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet*. 2007;370(9601):1757-1763. doi:10.1016/S0140-6736(07)61744-9

12. Vesikari T, Karvonen A, Prymula R, et al. Immunogenicity and safety of the human rotavirus vaccine Rotarix co-administered with routine infant vaccines following the vaccination schedules in Europe. *Vaccine*. 2010;28(32):5272-5279. doi:10.1016/j.vaccine.2010.05.057

13. Vesikari T, Itzler R, Karvonen A, et al. RotaTeq, a pentavalent rotavirus vaccine: efficacy and safety among infants in Europe. *Vaccine*. 2009;28(2):345-351. doi:10.1016/j.vaccine.2009.10.041

14. Vesikari T, Karvonen A, Bouckenooghe A, Suryakiran PV, Smolenov I, Han HH. Immunogenicity, reactogenicity and safety of the human rotavirus vaccine RIX4414 oral suspension (liquid formulation) in Finnish infants. *Vaccine*. 2011;29(11):2079-2084. doi:10.1016/j.vaccine.2011.01.004

15. Vesikari T, Clark HF, Offit PA, et al. Effects of the potency and composition of the multivalent human-bovine (WC3) reassortant rotavirus vaccine on efficacy, safety and immunogenicity in healthy infants. *Vaccine*. 2006;24(22):4821-4829. doi:10.1016/j.vaccine.2006.03.025

16. Kawamura N, Tokoeda Y, Oshima M, et al. Efficacy, safety and immunogenicity of RIX4414 in Japanese infants during the first two years of life. *Vaccine*. 2011;29(37):6335-6341. doi:10.1016/j.vaccine.2011.05.017

17. Iwata S, Nakata S, Ukae S, et al. Efficacy and safety of pentavalent rotavirus vaccine in Japan: a randomized, double-blind, placebo-controlled, multicenter trial. *Hum Vaccin Immunother*. 2013;9(8):1626-1633. doi:10.4161/hv.24846

18. Kim DS, Lee TJ, Kang JH, et al. Immunogenicity and safety of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine in healthy infants in Korea. *Pediatr Infect Dis J*. 2008;27(2):177-178. doi:10.1097/INF.0b013e31815aba79

19. Kim JS, Bae CW, Lee KY, et al. Immunogenicity, reactogenicity and safety of a human rotavirus vaccine (RIX4414) in Korean infants: a randomized, double-blind, placebo-controlled, phase IV study. *Hum Vaccin Immunother*. 2012;8(6):806-812. doi:10.4161/hv.19853

20. Phua KB, Lim FS, Lau YL, et al. Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: randomised, double-blind, controlled study. *Vaccine*. 2009;27(43):5936-5941. doi:10.1016/j.vaccine.2009.07.098

21. Phua KB, Lim FS, Lau YL, et al. Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomized clinical trial in an Asian population. *Vaccine*. 2012;30(30):4552-4557. doi:10.1016/j.vaccine.2012.03.030

22. Phua KB, Lim FS, Quak SH, et al. Efficacy, immunogenicity and safety of a human rotavirus vaccine RIX4414 in Singaporean infants. *Ann Acad Med Singap*. 2016;45(2):44-50.

23. Phua KB, Quak SH, Lee BW, et al. Evaluation of RIX4414, a live, attenuated rotavirus vaccine, in a randomized, double-blind, placebo-controlled phase 2 trial involving 2464 Singaporean infants. *J Infect Dis*. 2005;192(suppl 1):S6-S16. doi:10.1086/431511

24. Li RC, Huang T, Li Y, et al. Human rotavirus vaccine (RIX4414) efficacy in the first two years of life: a randomized, placebo-controlled trial in China. *Hum Vaccin Immunother*. 2014;10(1):11-18. doi:10.4161/hv.26319

25. Li RC, Huang T, Li Y, et al. Immunogenicity and reactogenicity of the human rotavirus vaccine, RIX4414 oral suspension, when co-administered with routine childhood vaccines in Chinese infants. *Hum Vaccin Immunother*. 2016;12(3):785-793. doi:10.1080/21645515.2015.1085143

26. Lau Y-L, Nelson EAS, Poon K-H, et al; Hong Kong Rotarix Study Group. Efficacy, safety and immunogenicity of a human rotavirus vaccine (RIX4414) in Hong Kong children up to three years of age: a randomized, controlled trial. *Vaccine*. 2013;31(18):2253-2259. doi:10.1016/j.vaccine.2013.03.001

27. Mo Z, Mo Y, Li M, et al. Efficacy and safety of a pentavalent live human-bovine reassortant rotavirus vaccine (RV5) in healthy Chinese infants: a randomized, double-blind, placebo-controlled trial. *Vaccine*. 2017;35(43):5897-5904. doi:10.1016/j.vaccine.2017.08.081

28. Mo Z, Ma X, Luo P, et al; V260-024 Study Group. Immunogenicity of pentavalent rotavirus vaccine in Chinese infants. *Vaccine*. 2019;37(13):1836-1843. doi:10.1016/j.vaccine.2019.02.018

29. Chang CC, Chang MH, Lin TY, Lee HC, Hsieh WS, Lee PI. Experience of pentavalent human-bovine reassortant rotavirus vaccine among healthy infants in Taiwan. *J Formos Med Assoc*. 2009;108(4):280-285. doi:10.1016/S0929-6646(09)60067-X

30. Xia S, Du J, Su J, et al. Efficacy, immunogenicity and safety of a trivalent live human-lamb reassortant rotavirus vaccine (LLR3) in healthy Chinese infants: a randomized, double-blind, placebo-controlled trial. *Vaccine*. 2020;38(46):7393-7400. doi:10.1016/j.vaccine.2020.04.038

31. Colgate ER, Haque R, Dickson DM, et al. Delayed dosing of oral rotavirus vaccine demonstrates decreased risk of rotavirus gastroenteritis associated with serum zinc: a randomized controlled trial. *Clin Infect Dis*. 2016;63(5):634-641. doi:10.1093/cid/ciw346

32. Zaman K, Sack DA, Yunus M, et al; Bangladeshi Rotavirus Vaccine study group. Successful co-administration of a human rotavirus and oral poliovirus vaccines in Bangladeshi infants in a 2-dose schedule at 12 and 16 weeks of age. *Vaccine*. 2009;27(9):1333-1339. doi:10.1016/j.vaccine.2008.12.059

33. Zaman K, Dang DA, Victor JC, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010;376(9741):615-623. doi:10.1016/S0140-6736(10)60755-6

34. Anh DD, Carlos CC, Thiem DV, et al. Immunogenicity, reactogenicity and safety of the human rotavirus vaccine RIX4414 (Rotarix™) oral suspension (liquid formulation) when co-administered with expanded program on immunization (EPI) vaccines in Vietnam and the Philippines in 2006-2007. *Vaccine*. 2011;29(11):2029-2036. doi:10.1016/j.vaccine.2011.01.018

35. Narang A, Bose A, Pandit AN, et al. Immunogenicity, reactogenicity and safety of human rotavirus vaccine (RIX4414) in Indian infants. *Hum Vaccin*. 2009;5(6):414-419. doi:10.4161/hv.5.6.8176

36. Bhandari N, Sharma P, Taneja S, et al; Rotavirus Vaccine Development Group. A dose-escalation safety and immunogenicity study of live attenuated oral rotavirus vaccine 116E in infants: a randomized, double-blind, placebo-controlled trial. *J Infect Dis*. 2009;200(3):421-429. doi:10.1086/600104

37. John J, Kawade A, Rongsen-Chandola T, et al. Active surveillance for intussusception in a phase III efficacy trial of an oral monovalent rotavirus vaccine in India. *Vaccine*. 2014;32(suppl 1):A104-A109. doi:10.1016/j.vaccine.2014.03.036

38. Bhandari N, Rongsen-Chandola T, Bavdekar A, et al; India Rotavirus Vaccine Group. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2014;383(9935):2136-2143. doi:10.1016/S0140-6736(13)62630-6

39. Kulkarni PS, Desai S, Tewari T, et al; SII BRV-PV author group. A randomized phase III clinical trial to assess the efficacy of a bovine-human reassortant pentavalent rotavirus vaccine in Indian infants. *Vaccine*. 2017;35(45):6228-6237. doi:10.1016/j.vaccine.2017.09.014

40. Tregnaghi MW, Abate HJ, Valencia A, et al; Rota-024 Study Group. Human rotavirus vaccine is highly efficacious when coadministered with routine expanded program of immunization vaccines including oral poliovirus vaccine in Latin America. *Pediatr Infect Dis J*. 2011;30(6):e103-e108. doi:10.1097/INF.0b013e3182138278

41. Linhares AC, Velázquez FR, Pérez-Schael I, et al; Human Rotavirus Vaccine Study Group. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. *Lancet*. 2008;371(9619):1181-1189. doi:10.1016/S0140-6736(08)60524-3

42. Salinas B, Pérez Schael I, Linhares AC, et al. Evaluation of safety, immunogenicity and efficacy of an attenuated rotavirus vaccine, RIX4414: a randomized, placebo-controlled trial in Latin American infants. *Pediatr Infect Dis J*. 2005;24(9):807-816. doi:10.1097/01.inf.0000178294.13954.a1

43. Ruiz-Palacios GM, Guerrero ML, Bautista-Márquez A, et al. Dose response and efficacy of a live, attenuated human rotavirus vaccine in Mexican infants. *Pediatrics*. 2007;120(2):e253-e261. doi:10.1542/peds.2006-2630

44. Justino MCA, Araújo EC, van Doorn L-J, et al. Oral live attenuated human rotavirus vaccine (Rotarix™) offers sustained high protection against severe G9P[8] rotavirus gastroenteritis during the first two years of life in Brazilian children. *Mem Inst Oswaldo Cruz*. 2012;107(7):846-853. doi:10.1590/S0074-02762012000700002

45. Christie CDC, Duncan ND, Thame KA, et al. Pentavalent rotavirus vaccine in developing countries: safety and health care resource utilization. *Pediatrics*. 2010;126(6):e1499-e1506. doi:10.1542/peds.2010-1240

46. Isanaka S, Guindo O, Langendorf C, et al. Efficacy of a low-cost, heat-stable oral rotavirus vaccine in Niger. *N Engl J Med*. 2017;376(12):1121-1130. doi:10.1056/NEJMoa1609462

47. Coldiron ME, Guindo O, Makarimi R, et al. Safety of a heat-stable rotavirus vaccine among children in Niger: data from a phase 3, randomized, double-blind, placebo-controlled trial. *Vaccine*. 2018;36(25):3674-3680. doi:10.1016/j.vaccine.2018.05.023

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

48. Madhi SA, Cunliffe NA, Steele D, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. *N Engl J Med*. 2010;362(4):289-298. doi:10.1056/NEJMoa0904797

49. Steele AD, Neuzil KM, Cunliffe NA, et al. Human rotavirus vaccine Rotarix™ provides protection against diverse circulating rotavirus strains in African infants: a randomized controlled trial. *BMC Infect Dis*. 2012;12:213. doi:10.1186/1471-2334-12-213

50. Steele AD, Reynders J, Scholtz F, et al. Comparison of 2 different regimens for reactogenicity, safety, and immunogenicity of the live attenuated oral rotavirus vaccine RIX4414 coadministered with oral polio vaccine in South African infants. *J Infect Dis*. 2010;202(suppl):S93-S100. doi:10.1086/653550

51. Cunliffe NA, Witte D, Ngwira BM, et al. Efficacy of human rotavirus vaccine against severe gastroenteritis in Malawian children in the first two years of life: a randomized, double-blind, placebo controlled trial. *Vaccine*. 2012;30(suppl 1):A36-A43. doi:10.1016/j.vaccine.2011.09.120

52. Rojas OL, Caicedo L, Guzmán C, et al. Evaluation of circulating intestinally committed memory B cells in children vaccinated with attenuated human rotavirus vaccine. *Viral Immunol*. 2007;20(2):300-311. doi:10.1089/vim.2006.0105

53. Armah GE, Sow SO, Breiman RF, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010;376(9741):606-614. doi:10.1016/S0140-6736(10)60889-6

54. Tapia MD, Armah G, Breiman RF, et al. Secondary efficacy endpoints of the pentavalent rotavirus vaccine against gastroenteritis in sub-Saharan Africa. *Vaccine*. 2012;30(suppl 1):A79-A85. doi:10.1016/j.vaccine.2012.01.022

55. Sow SO, Tapia M, Haidara FC, et al. Efficacy of the oral pentavalent rotavirus vaccine in Mali. *Vaccine*. 2012;30(suppl 1):A71-A78. doi:10.1016/j.vaccine.2011.11.094

56. Laserson KF, Nyakundi D, Feikin DR, et al. Safety of the pentavalent rotavirus vaccine (PRV), RotaTeq(®), in Kenya, including among HIV-infected and HIV-exposed infants. *Vaccine*. 2012;30(suppl 1):A61-A70. doi:10.1016/j.vaccine.2011.09.026

57. Georges-Courbot MC, Monges J, Siopathis MR, et al. Evaluation of the efficacy of a low-passage bovine rotavirus (strain WC3) vaccine in children in Central Africa. *Res Virol*. 1991;142(5):405-411. doi:10.1016/0923-2516(91)90008-Q

58. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med*. 2006;354(1):11-22. doi:10.1056/NEJMoa052434

59. Breiman RF, Zaman K, Armah G, et al. Analyses of health outcomes from the 5 sites participating in the Africa and Asia clinical efficacy trials of the oral pentavalent rotavirus vaccine. *Vaccine*. 2012;30(suppl 1):A24-A29. doi:10.1016/j.vaccine.2011.08.124

60. Block SL, Vesikari T, Goveia MG, et al; Pentavalent Rotavirus Vaccine Dose Confirmation Efficacy Study Group. Efficacy, immunogenicity, and safety of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine at the end of shelf life. *Pediatrics*. 2007;119(1):11-18. doi:10.1542/peds.2006-2058

61. Vesikari T, Matson DO, Dennehy P, et al; Rotavirus Efficacy and Safety Trial (REST) Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354(1):23-33. doi:10.1056/NEJMoa052664

62. Goveia MG, DiNubile MJ, Dallas MJ, Heaton PM, Kuter BJ; REST Study Team. Efficacy of pentavalent human-bovine (WC3) reassortant rotavirus vaccine based on breastfeeding frequency. *Pediatr Infect Dis J*. 2008;27(7):656-658. doi:10.1097/INF.0b013e318168d29e

63. Dennehy PH, Goveia MG, Dallas MJ, Heaton PM. The integrated phase III safety profile of the pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *Int J Infect Dis*. 2007;11(suppl 2):S36-S42. doi:10.1016/S1201-9712(07)60020-4

64. Vesikari T, Itzler R, Matson DO, et al. Efficacy of a pentavalent rotavirus vaccine in reducing rotavirus-associated health care utilization across three regions (11 countries). *Int J Infect Dis*. 2007;11(suppl 2):S29-S35. doi:10.1016/S1201-9712(07)60019-8

65. Cortese MM, Immergluck LC, Held M, et al. Effectiveness of monovalent and pentavalent rotavirus vaccine. *Pediatrics*. 2013;132(1):e25-e33. doi:10.1542/peds.2012-3804

66. Immergluck LC, Parker TC, Jain S, et al. Sustained effectiveness of monovalent and pentavalent rotavirus vaccines in children. *J Pediatr*. 2016;172:116-120.e1. doi:10.1016/j.jpeds.2016.01.042

67. Staat MA, Payne DC, Donauer S, et al; New Vaccine Surveillance Network (NVSN). Effectiveness of pentavalent rotavirus vaccine against severe disease. *Pediatrics*. 2011;128(2):e267-e275. doi:10.1542/peds.2010-3722

68. Tate JE, Mijatovic-Rustempasic S, Tam KI, et al. Comparison of 2 assays for diagnosing rotavirus and evaluating vaccine effectiveness in children with gastroenteritis. *Emerg Infect Dis*. 2013;19(8):1245-1252. doi:10.3201/eid1908.130461

69. Donauer S, Payne DC, Edwards KM, et al. Determining the effectiveness of the pentavalent rotavirus vaccine against rotavirus hospitalizations and emergency department visits using two study designs. *Vaccine*. 2013;31(24):2692-2697. doi:10.1016/j.vaccine.2013.03.072

70. Boom JA, Tate JE, Sahni LC, et al. Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States. *Pediatrics*. 2010;125(2):e199-e207. doi:10.1542/peds.2009-1021

71. Cortese MM, Leblanc J, White KE, et al. Leveraging state immunization information systems to measure the effectiveness of rotavirus vaccine. *Pediatrics*. 2011;128(6):e1474-e1481. doi:10.1542/peds.2011-1006

72. Doll MK, Buckeridge DL, Morrison KT, et al. Effectiveness of monovalent rotavirus vaccine in a high-income, predominant-use setting. *Vaccine*. 2015;33(51):7307-7314. doi:10.1016/j.vaccine.2015.10.118

73. de Palma O, Cruz L, Ramos H, et al. Effectiveness of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study. *BMJ*. 2010;340:c2825. doi:10.1136/bmj.c2825

74. Braeckman T, Van Herck K, Meyer N, et al; RotaBel Study Group. Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study. *BMJ*. 2012;345:e4752. doi:10.1136/bmj.e4752

75. Matthijnssens J, Zeller M, Heylen E, et al; RotaBel study group. Higher proportion of G2P[4] rotaviruses in vaccinated hospitalized cases compared with unvaccinated hospitalized cases, despite high vaccine effectiveness against heterotypic G2P[4] rotaviruses. *Clin Microbiol Infect*. 2014;20(10):O702-O710. doi:10.1111/1469-0691.12612

76. Castilla J, Beristain X, Martínez-Artola V, et al. Effectiveness of rotavirus vaccines in preventing cases and hospitalizations due to rotavirus gastroenteritis in Navarre, Spain. *Vaccine*. 2012;30(3):539-543. doi:10.1016/j.vaccine.2011.11.071

77. Walker JL, Andrews NJ, Atchison CJ, et al. Effectiveness of oral rotavirus vaccination in England against rotavirus-confirmed and all-cause acute gastroenteritis. *Vaccine X*. 2019;1:100005. doi:10.1016/j.jvacx.2019.100005

78. Oberle D, Hoffelner M, Pavel J, et al. Retrospective multicenter matched case-control study on the risk factors for intussusception in infants less than 1 year of age with a special focus on rotavirus vaccines—the German Intussusception Study. *Hum Vaccin Immunother*. 2020;16(10):2481-2494. doi:10.1080/21645515.2020.1726679

79. Gheorghita S, Birca L, Donos A, et al. Impact of rotavirus vaccine introduction and vaccine effectiveness in the Republic of Moldova. *Clin Infect Dis*. 2016;62(suppl 2):S140-S146. doi:10.1093/cid/civ1209

80. Snelling TL, Schultz R, Graham J, et al. Rotavirus and the indigenous children of the Australian outback: monovalent vaccine effective in a high-burden setting. *Clin Infect Dis*. 2009;49(3):428-431. doi:10.1086/600395

81. Carlin JB, Macartney KK, Lee KJ, et al. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program. *Clin Infect Dis*. 2013;57(10):1427-1434. doi:10.1093/cid/cit520

82. Maguire JE, Glasgow K, Glass K, et al. Rotavirus epidemiology and monovalent rotavirus vaccine effectiveness in Australia: 2010-2017. *Pediatrics*. 2019;144(4):e20191024. doi:10.1542/peds.2019-1024

83. Araki K, Hara M, Tsugawa T, et al. Effectiveness of monovalent and pentavalent rotavirus vaccines in Japanese children. *Vaccine*. 2018;36(34):5187-5193. doi:10.1016/j.vaccine.2018.07.007

84. Araki K, Hara M, Shimanoe C, Nishida Y, Matsuo M, Tanaka K. Case-control study of rotavirus vaccine effectiveness compared to test-negative controls or hospital controls. *J Epidemiol*. 2019;29(8):282-287. doi:10.2188/jea.JE20180054

85. Lopez AL, Daag JV, Esparagoza J, et al. Effectiveness of monovalent rotavirus vaccine in the Philippines. *Sci Rep*. 2018;8(1):14291. doi:10.1038/s41598-018-32595-9

86. Muhsen K, Anis E, Rubinstein U, et al. Effectiveness of rotavirus pentavalent vaccine under a universal immunization programme in Israel, 2011-2015: a case-control study. *Clin Microbiol Infect*. 2018;24(1):53-59. doi:10.1016/j.cmi.2017.04.018

87. Eraliev U, Latipov R, Tursunova D, et al. Rotavirus vaccine effectiveness and impact in Uzbekistan, the first country to introduce in central Asia. *Hum Vaccin Immunother*. 2021;17(2):503-509. doi:10.1080/21645515.2020.1776034

88. Chang WC, Yen C, Wu FT, et al. Effectiveness of 2 rotavirus vaccines against rotavirus disease in Taiwanese infants. *Pediatr Infect Dis J*. 2014;33(3):e81-e86. doi:10.1097/INF.0000000000000105

89. Fu C, Wang M, Liang J, He T, Wang D, Xu J. Effectiveness of Lanzhou lamb rotavirus vaccine against rotavirus gastroenteritis requiring hospitalization: a matched case-control study. *Vaccine*. 2007;25(52):8756-8761. doi:10.1016/j.vaccine.2007.10.036

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

90. Fu C, He Q, Xu J, et al. Effectiveness of the Lanzhou lamb rotavirus vaccine against gastroenteritis among children. *Vaccine*. 2012;31(1):154-158. doi:10.1016/j.vaccine.2012.10.078

91. Zhen SS, Li Y, Wang SM, et al. Effectiveness of the live attenuated rotavirus vaccine produced by a domestic manufacturer in China studied using a population-based case-control design. *Emerg Microbes Infect*. 2015;4(10):e64. doi:10.1038/emi.2015.64

92. Li J, Zhang Y, Yang Y, et al. Effectiveness of Lanzhou lamb rotavirus vaccine in preventing gastroenteritis among children younger than 5 years of age. *Vaccine*. 2019;37(27):3611-3616. doi:10.1016/j.vaccine.2019.03.069

93. Patel M, Pedreira C, De Oliveira LH, et al. Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among children in Nicaragua. *JAMA*. 2009;301(21):2243-2251. doi:10.1001/jama.2009.756

94. Mast TC, Khawaja S, Espinoza F, et al. Case-control study of the effectiveness of vaccination with pentavalent rotavirus vaccine in Nicaragua. *Pediatr Infect Dis J*. 2011;30(11):e209-e215. doi:10.1097/INF.0b013e31822a8527

95. Patel M, Pedreira C, De Oliveira LH, et al. Duration of protection of pentavalent rotavirus vaccination in Nicaragua. *Pediatrics*. 2012;130(2):e365-e372. doi:10.1542/peds.2011-3478

96. Gastañaduy PA, Contreras-Roldán I, Bernart C, et al. Effectiveness of monovalent and pentavalent rotavirus vaccines in Guatemala. *Clin Infect Dis*. 2016;62(suppl 2):S121-S126. doi:10.1093/cid/civ1208

97. Correia JB, Patel MM, Nakagomi O, et al. Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P[4] strains in Brazil. *J Infect Dis*. 2010;201(3):363-369. doi:10.1086/649843

98. Patel MM, Patzi M, Pastor D, et al. Effectiveness of monovalent rotavirus vaccine in Bolivia: case-control study. *BMJ*. 2013;346:f3726. doi:10.1136/bmj.f3726

99. Ichihara MYT, Rodrigues LC, Teles Santos CAS, et al. Effectiveness of rotavirus vaccine against hospitalized rotavirus diarrhea: a case-control study. *Vaccine*. 2014;32(23):2740-2747. doi:10.1016/j.vaccine.2014.01.007

100. Justino MCA, Linhares AC, Lanzieri TM, et al. Effectiveness of the monovalent G1P[8] human rotavirus vaccine against hospitalization for severe G2P[4] rotavirus gastroenteritis in Belém, Brazil. *Pediatr Infect Dis J*. 2011;30(5):396-401. doi:10.1097/INF.0b013e3182055cc2

101. Patel MM, López-Collada VR, Bulhões MM, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *N Engl J Med*. 2011;364(24):2283-2292. doi:10.1056/NEJMoa1012952

102. Pringle KD, Patzi M, Tate JE, et al. Sustained effectiveness of rotavirus vaccine against very severe rotavirus disease through the second year of life, Bolivia 2013-2014. *Clin Infect Dis*. 2016;62(suppl 2):S115-S120. doi:10.1093/cid/civ1026

103. Cotes-Cantillo K, Paternina-Caicedo A, Coronell-Rodríguez W, et al. Effectiveness of the monovalent rotavirus vaccine in Colombia: a case-control study. *Vaccine*. 2014;32(25):3035-3040. doi:10.1016/j.vaccine.2014.03.064

104. Beres LK, Tate JE, Njobvu L, et al. A preliminary assessment of rotavirus vaccine effectiveness in Zambia. *Clin Infect Dis*. 2016;62(suppl 2):S175-S182. doi:10.1093/cid/civ1206

105. Bar-Zeev N, Kapanda L, Tate JE, et al; VacSurv Consortium. Effectiveness of a monovalent rotavirus vaccine in infants in Malawi after programmatic roll-out: an observational and case-control study. *Lancet Infect Dis*. 2015;15(4):422-428. doi:10.1016/S1473-3099(14)71060-6

106. Groome MJ, Page N, Cortese MM, et al. Effectiveness of monovalent human rotavirus vaccine against admission to hospital for acute rotavirus diarrhoea in South African children: a case-control study. *Lancet Infect Dis*. 2014;14(11):1096-1104. doi:10.1016/S1473-3099(14)70940-5

107. Groome MJ, Tate JE, Arnold M, et al. Evaluation of intussusception after oral monovalent rotavirus vaccination in South Africa. *Clin Infect Dis*. 2020;70(8):1606-1612. doi:10.1093/cid/ciz431

108. Gastañaduy PA, Steenhoff AP, Mokomane M, et al. Effectiveness of monovalent rotavirus vaccine after programmatic implementation in Botswana: a multisite prospective case-control study. *Clin Infect Dis*. 2016;62(suppl 2):S161-S167. doi:10.1093/cid/civ1207

109. Mokomane M, Tate JE, Steenhoff AP, et al. Evaluation of the influence of gastrointestinal coinfections on rotavirus vaccine effectiveness in Botswana. *Pediatr Infect Dis J*. 2018;37(3):e58-e62. doi:10.1097/INF.0000000000001828

110. Armah G, Pringle K, Enweronu-Laryea CC, et al. Impact and effectiveness of monovalent rotavirus vaccine against severe rotavirus diarrhea in Ghana. *Clin Infect Dis*. 2016;62(suppl 2):S200-S207. doi:10.1093/cid/ciw014

111. Bonkoungou IJO, Aliabadi N, Leshem E, et al. Impact and effectiveness of pentavalent rotavirus vaccine in children <5 years of age in Burkina Faso. *Vaccine*. 2018;36(47):7170-7178. doi:10.1016/j.vaccine.2017.12.056

112. Tate JE, Ngabo F, Donnen P, et al. Effectiveness of pentavalent rotavirus vaccine under conditions of routine use in Rwanda. *Clin Infect Dis*. 2016;62(suppl 2):S208-S212. doi:10.1093/cid/civ1016

113. Mujuru HA, Burnett E, Nathoo KJ, et al. Monovalent rotavirus vaccine effectiveness against rotavirus hospitalizations among children in Zimbabwe. *Clin Infect Dis*. 2019;69(8):1339-1344. doi:10.1093/cid/ciy1096

114. Khagayi S, Omore R, Otieno GP, et al. Effectiveness of monovalent rotavirus vaccine against hospitalization with acute rotavirus gastroenteritis in Kenyan children. *Clin Infect Dis*. 2020;70(11):2298-2305. doi:10.1093/cid/ciz664

115. Wang FT, Mast TC, Glass RJ, Loughlin J, Seeger JD. Effectiveness of the pentavalent rotavirus vaccine in preventing gastroenteritis in the United States. *Pediatrics*. 2010;125(2):e208-e213. doi:10.1542/peds.2009-1246

116. Wang FT, Mast TC, Glass RJ, Loughlin J, Seeger JD. Effectiveness of an incomplete RotaTeq (RV5) vaccination regimen in preventing rotavirus gastroenteritis in the United States. *Pediatr Infect Dis J*. 2013;32(3):278-283. doi:10.1097/INF.0b013e318275328f

117. Shui IM, Baggs J, Patel M, et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. *JAMA*. 2012;307(6):598-604. doi:10.1001/jama.2012.97

118. Krishnarajah G, Kageleiry A, Korves C, Lefebvre P, Duh MS. Public health impact of Rotarix vaccination among commercially insured children in the United States. *Vaccine*. 2017;35(37):5065-5072. doi:10.1016/j.vaccine.2017.06.034

119. Hoffman V, Abu-Elyazeed R, Enger C, et al. Safety study of live, oral human rotavirus vaccine: a cohort study in United States health insurance plans. *Hum Vaccin Immunother*. 2018;14(7):1782-1790. doi:10.1080/21645515.2018.1450123

120. Gosselin V, Généreux M, Gagneur A, Petit G. Effectiveness of rotavirus vaccine in preventing severe gastroenteritis in young children according to socioeconomic status. *Hum Vaccin Immunother*. 2016;12(10):2572-2579. doi:10.1080/21645515.2016.1189038

121. Mrozek-Budzyn D, Kieltyka A, Majewska R, Augustyniak M. The effectiveness of rotavirus vaccine in preventing acute gastroenteritis during rotavirus seasons among Polish children. *Arch Med Sci*. 2016;12(3):614-620. doi:10.5114/aoms.2016.59935

122. Pérez-Vilar S, Díez-Domingo J, López-Lacort M, Martínez-Úbeda S, Martinez-Beneito MA. Effectiveness of rotavirus vaccines, licensed but not funded, against rotavirus hospitalizations in the Valencia region, Spain. *BMC Infect Dis*. 2015;15:92. doi:10.1186/s12879-015-0811-5

123. Gagneur A, Nowak E, Lemaitre T, et al; IVANHOE investigators. Impact of rotavirus vaccination on hospitalizations for rotavirus diarrhea: the IVANHOE study. *Vaccine*. 2011;29(21):3753-3759. doi:10.1016/j.vaccine.2011.03.035

124. Muhsen K, Chodick G, Goren S, Shalev V, Cohen D. The uptake of rotavirus vaccine and its effectiveness in preventing acute gastroenteritis in the community. *Vaccine*. 2010;29(1):91-94. doi:10.1016/j.vaccine.2010.10.010

125. Zaman K, Sack DA, Neuzil KM, et al. Effectiveness of a live oral human rotavirus vaccine after programmatic introduction in Bangladesh: a cluster-randomized trial. *PLoS Med*. 2017;14(4):e1002282. doi:10.1371/journal.pmed.1002282

126. Tharmaphornpilas P, Jiamsiri S, Boonchaiya S, et al. Evaluating the first introduction of rotavirus vaccine in Thailand: moving from evidence to policy. *Vaccine*. 2017;35(5):796-801. doi:10.1016/j.vaccine.2016.12.043

127. Vieira SCF, Gurgel RQ, Kirby A, et al. Acute diarrhoea in a community cohort of children who received an oral rotavirus vaccine in Northeast Brazil. *Mem Inst Oswaldo Cruz*. 2011;106(3):330-334. doi:10.1590/S0074-02762011000300012

128. Bar-Zeev N, King C, Phiri T, et al; VacSurv Consortium. Impact of monovalent rotavirus vaccine on diarrhoea-associated post-neonatal infant mortality in rural communities in Malawi: a population-based birth cohort study. *Lancet Glob Health*. 2018;6(9):e1036-e1044. doi:10.1016/S2214-109X(18)30314-0

129. Leshem E, Lopman B, Glass R, et al. Distribution of rotavirus strains and strain-specific effectiveness of the rotavirus vaccine after its introduction: a systematic review and meta-analysis. *Lancet Infect Dis*. 2014;14(9):847-856. doi:10.1016/S1473-3099(14)70832-1

130. Grimwood K, Lund JC, Coulson BS, Hudson IL, Bishop RF, Barnes GL. Comparison of serum and mucosal antibody responses following severe acute rotavirus gastroenteritis in young children. *J Clin Microbiol*. 1988;26(4):732-738. doi:10.1128/JCM.26.4.732-738.1988

131. Velázquez FR, Matson DO, Guerrero ML, et al. Serum antibody as a marker of protection against natural rotavirus infection and disease. *J Infect Dis*. 2000;182(6):1602-1609. doi:10.1086/317619

132. Soares-Weiser K, Bergman H, Henschke N, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Syst Rev*. 2019;2019(10).

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022

133. Hungerford D, Smith K, Tucker A, et al. Population effectiveness of the pentavalent and monovalent rotavirus vaccines: a systematic review and meta-analysis of observational studies. *BMC Infect Dis*. 2017;17(1):569. doi:10.1186/s12879-017-2613-4

134. Lamberti LM, Ashraf S, Walker CL, Black RE. A systematic review of the effect of rotavirus vaccination on diarrhea outcomes among children younger than 5 Years. *Pediatr Infect Dis J*. 2016;35(9):992-998. doi:10.1097/INF.0000000000001232

135. Burnett E, Parashar UD, Tate JE. Global impact of rotavirus vaccination on diarrhea hospitalizations and deaths among children <5 years old: 2006-2019. *J Infect Dis*. 2020;222(10):1731-1739. doi:10.1093/infdis/jiaa081

136. Lu HL, Ding Y, Goyal H, Xu HG. Association between rotavirus vaccination and risk of intussusception among neonates and infants: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(10):e1912458. doi:10.1001/jamanetworkopen.2019.12458

137. WHO. Global advisory committee on vaccine safety, 11-12 December 2013. *wkly epidemiol rec*. 2014;89(7):53-60.

138. Carlin JB, Macartney KK, Lee KJ, et al. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program. *Clin Infect Dis*. 2013;57(10):1427-1434. doi:10.1093/cid/cit520

139. Hasso-Agopsowicz M, Ladva CN, Lopman B, et al; Global Rotavirus Surveillance Network and Rotavirus Age Study Collaborators. Global review of the age distribution of rotavirus disease in children aged <5 years before the introduction of rotavirus vaccination. *Clin Infect Dis*. 2019;69(6):1071-1078. doi:10.1093/cid/ciz060

140. Clark A, van Zandvoort K, Flasche S, et al. Efficacy of live oral rotavirus vaccines by duration of follow-up: a meta-regression of randomised controlled trials. *Lancet Infect Dis*. 2019;19(7):717-727. doi:10.1016/S1473-3099(19)30126-4

141. Jonesteller CL, Burnett E, Yen C, Tate JE, Parashar UD. Effectiveness of rotavirus vaccination: a systematic review of the first decade of global postlicensure data, 2006-2016. *Clin Infect Dis*. 2017;65(5):840-850. doi:10.1093/cid/cix369

142. Dennehy PH, Vesikari T, Matson DO, et al. Efficacy of the pentavalent rotavirus vaccine, RotaTeq® (RV5), between doses of a 3-dose series and with less than 3 doses (incomplete regimen). *Hum Vaccin*. 2011;7(5):563-568. doi:10.4161/hv.7.5.15406

143. Todd S, Page NA, Duncan Steele A, Peenze I, Cunliffe NA. Rotavirus strain types circulating in Africa: review of studies published during 1997-2006. *J Infect Dis*. 2010;202(suppl):S34-S42. doi:10.1086/653555

144. Santos N, Hoshino Y. Global distribution of rotavirus serotypes/genotypes and its implication for the development and implementation of an effective rotavirus vaccine. *Rev Med Virol*. 2005;15(1):29-56. doi:10.1002/rmv.448

145. Nakagomi T, Cuevas LE, Gurgel RG, et al. Apparent extinction of non-G2 rotavirus strains from circulation in Recife, Brazil, after the introduction of rotavirus vaccine. *Arch Virol*. 2008;153(3):591-593. doi:10.1007/s00705-007-0028-z

146. Carvalho-Costa FA, Araújo IT, Santos de Assis RM, et al. Rotavirus genotype distribution after vaccine introduction, Rio de Janeiro, Brazil. *Emerg Infect Dis*. 2009;15(1):95-97. doi:10.3201/eid1501.071136

147. Hungerford D, Allen DJ, Nawaz S, et al. Impact of rotavirus vaccination on rotavirus genotype distribution and diversity in England, September 2006 to August 2016. *Euro Surveill*. 2019;24(6). doi:10.2807/1560-7917.ES.2019.24.6.1700774

148. Matthijnssens J, Bilcke J, Ciarlet M, et al. Rotavirus disease and vaccination: impact on genotype diversity. *Future Microbiol*. 2009;4(10):1303-1316. doi:10.2217/fmb.09.96

149. Vesikari T, Matson DO, Dennehy P, et al; Rotavirus Efficacy and Safety Trial (REST) Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354(1):23-33. doi:10.1056/NEJMoa052664

150. Perez-Schael I, Salinas B, Tomat M, et al. Efficacy of the human rotavirus vaccine RIX4414 in malnourished children. *J Infect Dis*. 2007;196(4):537-540. doi:10.1086/519687

151. Naylor C, Lu M, Haque R, et al; PROVIDE study teams. Environmental enteropathy, oral vaccine failure and growth faltering in infants in Bangladesh. *EBioMedicine*. 2015;2(11):1759-1766. doi:10.1016/j.ebiom.2015.09.036

152. Taniuchi M, Platts-Mills JA, Begum S, et al. Impact of enterovirus and other enteric pathogens on oral polio and rotavirus vaccine performance in Bangladeshi infants. *Vaccine*. 2016;34(27):3068-3075. doi:10.1016/j.vaccine.2016.04.080

153. Yang H, Luo G, Zeng Y, et al. The distinct impact of maternal antibodies on the immunogenicity of live and recombinant rotavirus vaccines. *Vaccine*. 2019;37(30):4061-4067. doi:10.1016/j.vaccine.2019.05.086

154. Sindhu KN, Cunliffe N, Peak M, et al. Impact of maternal antibodies and infant gut microbiota on the immunogenicity of rotavirus vaccines in African, Indian and European infants: protocol for a prospective cohort study. *BMJ Open*. 2017;7(3):e016577. doi:10.1136/bmjopen-2017-016577

155. Soares-Weiser K. Rotavirus vaccine schedules: a systematic review of safety and efficacy from randomized controlled trials and observational studies of childhood schedules using RV1 and RV5 vaccines, report to WHO/Initiative for Vaccine Research 2012. Published 2012. Accessed March 5, 2021. https://www.who.int/immunization/sage/meetings/2012/april/Soares_K_et_al_SAGE_April_rotavirus.pdf

156. Lopman BA, Pitzer VE, Sarkar R, et al. Understanding reduced rotavirus vaccine efficacy in low socio-economic settings. *PLoS One*. 2012;7(8):e41720. doi:10.1371/journal.pone.0041720

157. Gladstone BP, Ramani S, Mukhopadhya I, et al. Protective effect of natural rotavirus infection in an Indian birth cohort. *N Engl J Med*. 2011;365(4):337-346. doi:10.1056/NEJMoa1006261

158. Bar-Zeev N, Tate JE, Pecenka C, et al; VACSURV Consortium. Cost-effectiveness of monovalent rotavirus vaccination of infants in Malawi: a postintroduction analysis using individual patient-level costing data. *Clin Infect Dis*. 2016;62(suppl 2):S220-S228. doi:10.1093/cid/civ1025

159. Bruijning-Verhagen P, van Dongen JAP, Verberk JDM, et al. Updated cost-effectiveness and risk-benefit analysis of two infant rotavirus vaccination strategies in a high-income, low-endemic setting. *BMC Med*. 2018;16(1):168. doi:10.1186/s12916-018-1134-3

160. van Hoek AJ, Ngama M, Ismail A, et al. A cost effectiveness and capacity analysis for the introduction of universal rotavirus vaccination in Kenya: comparison between Rotarix and RotaTeq vaccines. *PLoS One*. 2012;7(10):e47511. doi:10.1371/journal.pone.0047511

161. Debellut F, Jaber S, Bouzya Y, et al. Introduction of rotavirus vaccination in Palestine: An evaluation of the costs, impact, and cost-effectiveness of Rotarix and Rotavac. *PLoS One*. 2020;15(2):e0228506. doi:10.1371/journal.pone.0228506

162. Karafillakis E, Hassounah S, Atchison C. Effectiveness and impact of rotavirus vaccines in Europe, 2006-2014. *Vaccine*. 2015;33(18):2097-2107. doi:10.1016/j.vaccine.2015.03.016

163. Rha B, Tate JE, Payne DC, et al. Effectiveness and impact of rotavirus vaccines in the United States: 2006-2012. *Expert Rev Vaccines*. 2014;13(3):365-376. doi:10.1586/14760584.2014.877846

© 2021 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 08/26/2022