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Effectiveness of Lanzhou lamb rotavirus vaccine in preventing gastroenteritis among children younger than 5 years of age

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ABSTRACT

Background: Lanzhou Lamb rotavirus (LLR) vaccine was licensed in China in 2000. It was the only vaccine available in private market before 2018. However, the data about the post-marketing effectiveness is very limited. To assess the vaccine effectiveness (VE), we conducted a case-control study based on the hospital surveillance system in Beijing from 2015 to 2017.

Methods: Seven hospitals located in seven districts in Beijing, from October 1, 2015, to March 31, 2017, were included. The VE of LLR vaccine was assessed in laboratory-confirmed rotavirus infection among children younger than five years old through a case-control design, using rotavirus-negative cases as controls. LLR vaccination was documented from a vaccination registry. VE was estimated adjusting for age group, gender, study site, the month of illness onset and interval days between illness onset to sampling through a logistic regression model.

Results: A total of 598 cases and 1766 controls were included in this study. The vaccine average coverage rate during 2015–2017 among children younger than five years old was 10.8% in Beijing. The adjusted VE for LLR vaccine of 1 dose versus 0 dose was 34.9% (95%CI, 5.3–55.3). We also obtained the adjusted VE of 87.7% (95%CI, 32.7–97.8) for patients with the severity score ≥11, 36.2% (95%CI, 4.7–57.3) for children of 2–35 months age group and 40.8% (95%CI, 7.8–61.9) against G9 rotavirus infection. Vaccinated cases were less likely to have watery stool (OR = 0.42) and have diarrhea longer than 5 days (OR = 0.47) than unvaccinated cases.

Discussion: LLR vaccine conferred protection against rotavirus disease. Children who were vaccinated presented with less severe clinical manifestations. An immunization schedule of receiving all three doses in the first year should be preferred.

1. Introduction

Rotavirus infection is the leading cause of diarrhea-associated morbidity and mortality among children younger than 5 years throughout the world [1]. It accounts for more than 258 million episodes of diarrhea and was responsible for an estimated 128,500 deaths among children younger than 5 years all over the world in 2016 [1]. In China, among children younger than 5 years, about ~40% and ~30% of diarrhea-related hospitalizations and outpatient visits were caused by rotavirus [2]. The burden of rotavirus gastroenteritis in China is enormous and was estimated to cost about $61.4 million per year [3].

Introduction of vaccines against rotavirus disease is the most potent intervention to alleviate the diarrhea burden so far. The Lanzhou lamb rotavirus (LLR) vaccine was developed by the Lanzhou Institute of Biological Products and was the only one licensed in China in 2000 [4]. It is a live, attenuated oral rotavirus vaccine consisting of serotype G10P[12] and is recommended for children aged 2–36 months, one dose between 6 and 12 months of age followed by yearly boosters [5].

Due to the lack of a proper phase III clinical trial, few data about the efficacy of the LLR vaccine are available. The effectiveness of LLR vaccine was reported in several studies which were performed in Guangzhou and Hebei province during 2007–2012, but with inconsistent result which was from 35.0 to 73.3% [6–8]. On the other hand, since the VE is closely associated with the local economic conditions, it's urgent and necessary to study the VE in Beijing.

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We conducted a study using a case-control design to assess the VE of the LLR vaccine to prevent laboratory-confirmed gastroenteritis in children 2–59 months of age.

2. Material and methods

2.1. Enrollment of subjects, information and sample collection

This case-control study was performed in seven hospitals located in seven districts in Beijing from 1 October 2015 to 1 March 2017. The seven hospitals are either the largest or having the most patient visits in the area. Each month, the first 30 patients with acute gastroenteritis diagnosed by doctors from each surveillance hospitals were invited to participate in this study. After obtaining informed consent from parents or legal guardian, patients' information was collected using a self-designed questionnaire, including demographic information, clinical information and epidemiological information. Beijing Management System of Information on Immunization Program was used to collect documented rotavirus vaccination records by searching name, birthdate, gender, residential address, parents phone numbers. A stool specimen was collected from each of the 30 enrolled cases at the first medical consultation. District CDCs were responsible for primary detection of rotavirus by rRT-PCR kit (Bioperfectus technologies CO., LTD) and sending collected samples and information of patients to Beijing CDC each month. Beijing CDC was responsible for genotyping of rotavirus [9,10], detection of norovirus [11], astrovirus [12] and adenovirus [13].

2.2. Definition and selection of cases and controls

Acute gastroenteritis case was defined as people who have the symptoms of diarrhea ($\geq$3 episodes within 24 h) and/or vomiting ($\geq$1 episode within 24 h). In this study, cases were children aged under five years old, with acute gastroenteritis symptoms and their fecal specimens were rotavirus-positive not considering the mixed infection with other agents. The controls were those children with acute gastroenteritis symptoms whose fecal specimens were rotavirus-negative not considering the mixed infection with other agents. Patients, whose vaccination status could not be determined, were younger than 2 months or older than 60 months were excluded. Patients who reported having a contraindication to rotavirus vaccination or received a rotavirus vaccine within 14 days before symptom onset were excluded from the study.

In order to ensure the study result was comparable with other studies, vesikari clinical severity scoring system was used to define the severity cases. Severe rotavirus gastroenteritis was defined as the score $\geq$11 on this established 20-point severity scoring system on the basis of the intensity and duration of symptoms of fever, vomiting, diarrhea, degree of dehydration, and treatment needed [14]. Non-severe cases were defined as the score lower than 11.

2.3. Sensitivity analysis

We assessed sensitivity of VE estimates to control group inclusion criteria by repeating the regression analyses with case group that was rotavirus-positive without mixed infection with norovirus, astrovirus and adenovirus, with control groups that (1) were negative for rotavirus, and (2) were negative for rotavirus but excluded all norovirus-, astrovirus- and adenovirus-positive cases.

2.4. Statistical analysis

Questionnaire and laboratory data were entered using EpiData Software and statistical analysis was performed using SPSS 19 software (IBM SPSS, Inc., Chicago, IL, USA). Categorical variables were described using frequencies and percentages. Chi-square test was performed to assess differences in the characteristics between different groups. p value of less than 0.05 was considered as statistically significant.

The adjusted odds ratios and 95% confidence intervals (CIs) were calculated by multivariate logistic regression and were adjusted for characteristics, such as age group, gender, illness onset month and interval days of illness onset to sampling and study site. The enter method was used for screening of variables, and goodness-of-fit tests (Hosmer-Lemeshow) were performed on the logistic model. VE was calculated using the following formula: [VE = (1 − odds ratio) × 100]. All tests were 2-sided and p values < 0.05 were considered significant.

2.5. Ethics statement

This study was approved by institutional review board and human research ethics committee of Beijing CDC. The agreement and verbal informed consent was obtained from parents or legal guardian for all the children.

3. Results

3.1. Characteristics of cases and controls

Between 1 October 2015 and 31 March 2017, a total of 2775 patients presenting to the seven selected hospitals in seven districts in Beijing were screened (Fig. 1). Patients whose vaccination status could not be determined (n = 249), were younger than 2 months (n = 136) or older than 60 months (n = 26) were excluded. Therefore a total of 2364 patients meeting the inclusion criteria were enrolled during the study period and were included in the vaccine effectiveness study.

Of the 2364 patients, 598 (25.3%) were positive of rotavirus, 283 (12.0%) samples were positive for norovirus, 129 (5.4%) for adenovirus, 93 (3.9%) for astrovirus. The predominant serotype of rotavirus was G9 (403/598, 67.4%), followed by G3 (76/598, 12.7%) and G2 (42/598, 7.0%). A total of 598 (male: 387, 64.7%) rotavirus cases (median age: 14 months with IQR: 10–20 months) and 1766 (male: 1035, 58.6%) controls (median age: 12 months with IQR: 6–22 months) were included in the effectiveness study. Detection rate of rotavirus infections varied by gender, age group, study site, interval from illness onset to sampling and the illness onset month (p < 0.05) (Table 1). The highest rotavirus-positive rate was 36.0% for 12–23 month group which was followed by 28.4% for 24–35 month group and 26.2% for children of 6–11 month group.

Among the laboratory-confirmed rotavirus infected cases, 127 (5.4%) cases were co-infected. 84 (66.1%) were rotavirus with norovirus, 13 (10.2%) for rotavirus with adenovirus, 12 (9.4%) for rotavirus with norovirus and adenovirus, 14 (11.0%) for rotavirus with astrovirus, 4 (3.1%) were for rotavirus with norovirus and astrovirus.

3.2. Vaccination

Among the 2364 cases, 255 patients (10.8%) (221 children received one LLR vaccine dose, 31 children received 2 doses, 3 children received 3 doses) were confirmed to have received at least one dose.

The vaccination coverage varied substantially by age: with 1.1% in children 3–5 months, 4.1% in 6–11 months, 14.7% in 12–23 months and about 20.0% for 24–59 months. The vaccine coverage was similar between the male and female (10.4% vs. 11.4%, p = 0.466), whereas significantly different between the patients

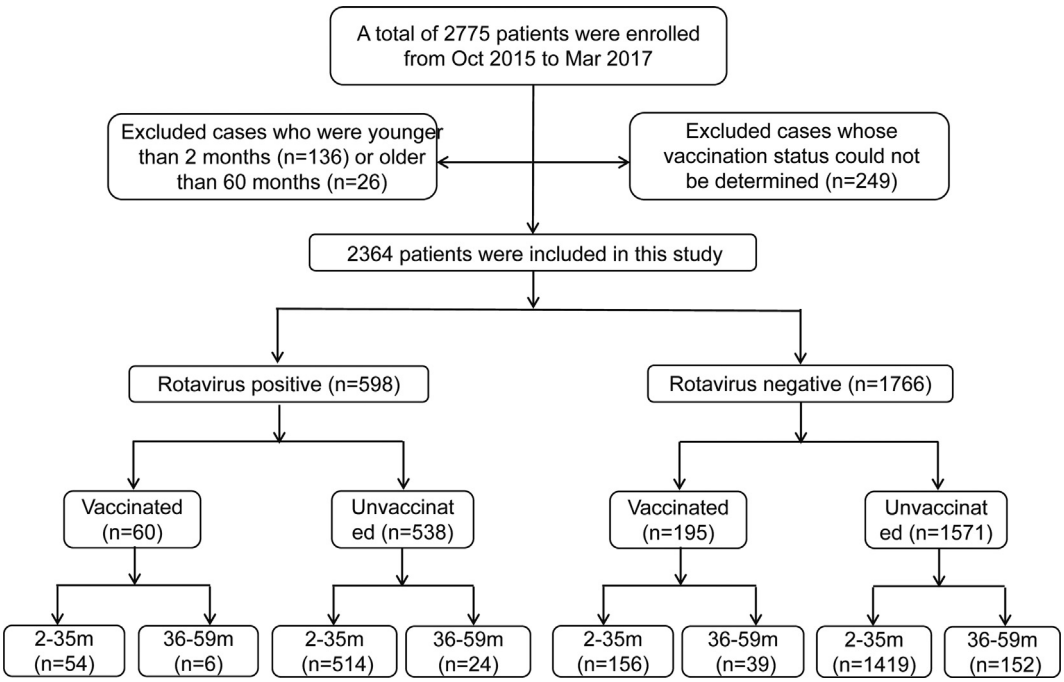

Fig. 1. The flow chart of enrolled subjects in the case-control study for estimating rotavirus vaccine effectiveness in Beijing, China, during 2015–2017.

within 3 days after illness onset and those longer than 3 days (12.0% vs 5.9%, $p < 0.001$). The proportion of vaccinated children was statistically different across seven districts (ranging from 6.2 to 19.6%, $p < 0.001$) and the months of vaccination (ranging from 2.7% to 14.8%, $p = 0.031$).

3.3. Vaccine effectiveness

Overall, 598 rotavirus cases and 1766 controls were included in the effectiveness study, and a protection rate of 34.9% (95%CI, 5.3–55.3%) was identified after adjusted for age groups, gender, study sites, the month of illness onset and interval days between illness onset to sampling (Table 2). An estimate of adjusted VE among patients with the severity score <11 and ≥11 was 11.7% (95%CI, −42.5–45.4%) and 87.7% (95%CI, 32.7–97.8%), respectively. The estimate of adjusted VE among patients of 2–35 months group and 36–59 months group were 36.2% (95%CI, 4.7–57.3%) and −1.6% (95%CI, −224.5–68.2%), respectively. Because the majority of rotavirus gastroenteritis cases were caused by the G9 serotype during the study period, a subgroup analysis was performed to estimate the protection against any G9 serotype rotavirus gastroenteritis and an estimate of VE of 40.8% (95%CI, 7.8–61.9%) was identified.

The sensitivity of VE estimates was assessed. Using rotavirus-positive cases without mixed infection with norovirus, astrovirus and adenovirus as the case, (1) using rotavirus-negative cases as the control, the VE was 41.2% (95%CI, 5.5–63.4%), (2) using rotavirus-negative cases but excluded all norovirus-, astrovirus- and adenovirus-positive cases as the control, the VE was 44.0% (95% CI, 14.7–63.3%).

The characteristics of clinical symptoms between vaccinated and unvaccinated confirmed rotavirus infection cases were compared (Table 3). Two relevant differences in the clinical system were found. In univariate analysis, vaccinated cases were significantly less likely to have watery stool (36.4% vs 51.1%, $p = 0.038$) and less likely to have a diarrhea longer than five days (32.7% vs 56.5%, $p = 0.001$). We also evaluated the odds ratio of clinical characteristics among different groups using vaccination status as predictor through a multivariate analysis. After adjusting for characteristics (gender, age, study site, onset month, interval between illness onset to sampling), compared to unvaccinated cases, the odds ratio of having watery stool and diarrhea duration longer than five days among vaccinated cases were 0.416 (95%CI, 0.219–0.791) and 0.466 (95%CI, 0.220–0.988), respectively. The odds ratio of presenting any other symptoms did not significantly differ by vaccination status.

4. Discussion

In this study, we analyzed the vaccination information for laboratory-confirmed rotavirus gastroenteritis cases in children 2–59 months from 2015 to 2017. Vaccine protection against rotavirus gastroenteritis was demonstrated by a case-control study in a hospital-based surveillance. The VE for 1 dose versus 0 was 34.9% after adjusting for age groups, gender, study sites, the month of illness onset and interval days between illness onset to sampling. This result was similar with Zhen's study [8] in which the VE of LLR vaccine was 35%, but was slightly lower than the VE estimate (43.8%) from a case-control study performed in 2009–2011 in Guangzhou, China [7]. Different rotavirus test methods and different factors adjusted in the logistic regression might have attributed to the different VE.

Since the major epidemic strains of rotavirus have changed in different years in the same area [3], an ideal vaccine should possess the potent property of protecting people against gastroenteritis caused by multiple serotype rotavirus. In the current study, though the LLR vaccine was animal sourced and characterized as G10P[12], it appeared to confer cross-protection against infection caused by rotavirus serotype G9 which was the major serotype during 2015 through 2017 in Beijing. According to Zhen's study [8], high VE estimate of LLR vaccine was found against rotavirus gastroenteritis caused by serotype G3 which was the predominant serotype during 2011–2012 in Hebei province. Base on the above results, we concluded that LLR vaccine could induce cross-protection against gastroenteritis caused by both G9 and G3 serotype rotavirus. It was because the limited number of confirmed rotavirus cases that

Table 1
Participant characteristics for estimates of rotavirus vaccine effectiveness in Beijing, October 1, 2015, to March 31, 2017.

Characteristics	Test-positive (n = 598) N (%)	Test-negative (n = 1766) N (%)	*p*-value[a]	Vaccinated (n = 255) N (%)	Not vaccinated (n = 2109) N (%)	*p*-value[a]
District						
Fengtai	102(17.1)	301(17.0)	**<0.001**	79 (31.0)	324 (15.4)	**<0.001**
Xicheng	94(15.7)	381(21.6)		29(11.4)	446(21.1)	
Changping	76(12.7)	182(10.3)		16(6.3)	242(11.5)	
Daxing	23(3.8)	165(9.3)		23(9.0)	165(7.8)	
Huairou	135(22.6)	194(16.6)		49(19.2)	380(18.0)	
Shunyi	26(4.3)	102(5.8)		27(10.6)	101(4.8)	
Tongzhou	142(23.7)	341(19.3)		32(12.5)	451(21.4)	
Age groups (months)						
0–5	36(6.0)	417(23.6)	**<0.001**	5(2.0)	448(21.2)	**<0.001**
6–11	146(24.4)	411(23.3)		23(9.0)	534(25.3)	
12–23	305(51.0)	543(30.7)		125(49.0)	723(34.3)	
24–35	81(13.5)	204(11.6)		57(22.4)	228(10.8)	
36–59	30(5.0)	191(10.8)		45(17.6)	176(8.3)	
Gender						
Male	387(64.7)	1035(58.6)	**0.008**	148(58.0)	1274(60.4)	0.466
Female	211(35.3)	731(41.4)		107(42.0)	835(39.6)	
Illness onset to sampling						
0–3 days	516(86.3)	1374(77.8)	**<0.001**	227(89.0)	1663(78.9)	**<0.001**
≧4 days	82(13.7)	392(22.2)		28(11.0)	446(21.1)	
Oneset month						
Jan	128(21.4)	86(4.9)	**<0.001**	20(7.8)	194(9.2)	**0.031**
Feb	123(20.6)	107(6.1)		26(10.2)	204(9.7)	
Mar	69(11.5)	139(7.9)		19(7.5)	189(9.0)	
Apr	24(4.0)	117(6.6)		15(5.9)	126(6.0)	
May	18(3.0)	155(8.8)		25(9.8)	148(7.0)	
Jun	5(0.8)	164(9.3)		25(9.8)	144(6.8)	
Jul	1(0.2)	183(10.4)		26(10.2)	158(7.5)	
Aug	1(0.2)	173(9.8)		16(6.3)	158(7.5)	
Sep	2(0.3)	148(8.4)		4(1.6)	146(6.9)	
Oct	6(1.0)	167(9.5)		14(5.5)	159(7.5)	
Nov	65(10.9)	172(9.7)		27(10.6)	210(10.0)	
Dec	156(26.1)	155(8.8)		38(14.9)	273(12.9)	
Rotavirus type						
G9	403(67.4)					
G3	76(12.7)					
G2	42(7.0)					

The bold values mean significant difference was obtained between compared groups.
[a] *p*-values estimated by chi-squared tests.

Table 2
Percentage vaccinated with rotavirus vaccine by cases and controls, with estimates of VE by all gastroenteritis cases, severity score, age groups and genotype of rotavirus in Beijing, October 1, 2015, to March 31, 2017.

Characteristics	Rotavirus positive vaccinated (%)	Rotavirus negative vaccinated (%)	Unadjusted VE% (95% CI)	*p-value*	Adjusted VE% (95% CI)[a]	*p-value*
All gastroenteritis cases	60/255(23.5)	195/255(76.5)	10.2(-21.9, 33.8)	0.492	**34.9(5.3, 55.3)**	**0.025**
Severity score						
<11	40/153(26.1)	113/153(73.9)	−9.2(-60.7, 25.7)	0.654	11.7(-42.5, 45.4)	0.609
≥11	5/10(50.0)	5/10(50.0)	53.3(-68.7, 87.1)	0.402	**87.7(32.7, 97.8)**	**0.016**
Age group (month)						
2–35	54/210(25.7)	156/210(74.3)	4.4(−32.3, 31.0)	0.785	**36.2(4.7, 57.3)**	**0.028**
36–59	6/45(13.3)	39/45(86.7)	2.6(−154.8, 62.7)	0.958	−1.6(-224.5, 68.2)	0.979
Subtype						
G9	38/233(16.3)	195/233(83.7)	16.1(-20.9, 41.8)	0.346	**40.8(7.8, 61.9)**	**0.020**

The bold values mean significant difference was obtained between compared groups.
[a] Adjusted for age groups, gender, study sites, the month of illness onset and interval days between illness onset to sampling.

the VE estimates against rotavirus gastroenteritis caused by some other serotype rotavirus weren't demonstrated. In 2018 April, Rotateq (Merck&Co., Inc. Whitehouse Station, New Jersey), a pentavalent vaccine (containing G1-4 and P[8]) [15], was approved by National Medical Products Administration(NMPA). What catch our attention is that this vaccine doesn't have G9 serotype which is the dominant rotavirus serotype in China. It has been reported that apart from homotypic protection, broader heterotypic protection including good cross protection against G9 strains developed by this vaccine as well [16–18]. We should pay close attention to the VE of this new vaccine in China.

Compared with other diarrhea causative pathogens, rotavirus dominated during the first two years of life [19]. In Beijing, the rotavirus infection rate was 34.1% in children younger than

Table 3
Comparisons of clinical symptoms between vaccinated and unvaccinated confirmed rotavirus infection cases in Beijing, October 1, 2015 to March 31, 2017.

Clinical presentations	Vaccinated	Not vaccinated	Total	Unadjusted OR (95%CI)	*p-value*	Adjusted OR[a] (95%CI)	*p-value*
Fever[b]							
<38.4	35(72.9)	236(62.6)	271	0.6 (0.3–1.2)	0.161	0.7 (0.4–1.5)	0.369
≧38.4	13(27.1)	141(37.4)	154				
Stool							
Loose	35(63.6)	253(48.9)	284	**0.5(0.3–1.0)**	**0.038**	**0.4 (0.2–0.8)**	**0.008**
watery stool	20(36.4)	264(51.1)	288				
Duration of Vomiting (days)[c]							
0	29(52.7)	254(49.6)	283	0.9(0.5–1.5)	0.660	0.8 (0.4–1.6)	0.576
≧1	26(47.3)	258(50.4)	284				
Duration of diarrhea (days)[c]							
1–4	35(67.3)	225(43.5)	260	**0.4(0.2–0.7)**	**0.001**	**0.5(0.2–1.0)**	**0.046**
≧5	17(32.7)	292(56.5)	309				
Diarrhea times in one day[c]							
3	23(41.8)	182(35.3)	205	0.8(0.4–1.3)	0.336	0.7 (0.4–1.4)	0.343
≧4	32(58.2)	334(64.7)	366				
Vomiting times in one day[c]							
0	29(52.7)	254(49.7)	283	0.9(0.5–1.5)	0.670	0.8 (0.4–1.6)	0.576
≧1	26(47.3)	257(50.3)	283				

The bold values mean significant difference was obtained between compared groups.
[a] Adjusted for age groups, gender, study sites, the month of illness onset and interval days between illness onset to sampling.
[b] Temperature was divided into two groups according to the vesikari clinical severity scoring system.
[c] Cases were divided into two groups according to the median.

11 months and it reached 70.1% in children younger than 23 months. Age groups under three years accounted for about 98% of the total confirmed rotavirus infection [20]. Widespread use of rotavirus vaccine would be the most effective way to decrease this disease. However, only 5.2% children were vaccinated in the first year of their life. 90% of the children who have been inoculated with LLR vaccine received only one dose. Low inoculation rate and incomplete vaccination course have influenced the protection effectiveness of vaccine. Moreover, the immunization schedule plays very important role in protecting people from infection. Since rotavirus is the dominant diarrhea causative pathogens during the first two years of life, we recommend that the first dose vaccine should be inoculated as early as possible. An immunization schedule of receiving all the three doses in the first year should be preferred.

In this study, the LLR vaccine was effective to protect people from severe rotavirus infection (Vesikari scale value was equal or above 11). This was consistent with other published studies about LLR vaccine, in which higher VE estimate was got in severe cases compared with moderate and mild patients [21,22]. However among the cases whose vesikari scale value was below 11, the rotavirus didn't show high protection. We think two factors might attribute to this result. First, the limited size of cases had resulted in wide confidence intervals. Second, the protection effect for this vaccine was not satisfactory against moderate and mild patients.

In combination with laboratory assays, the vesikari clinical severity scoring system was recognized as the most accurate system for identifying the endpoint in rotavirus vaccine effectiveness evaluation [14]. Diarrhea, vomiting and dehydration were important clinical presentations in rotavirus infection and were used as scoring parameters in the severity scoring system. In this study, vaccinated cases were less likely presenting watery stool and had shorter diarrhea duration. From this result, we found that although breakthrough infections do exist, compared to the cases without vaccination, children who are vaccinated prefer to present less severe clinical forms of the disease.

There are several limitations in this study. First, not included in the national immunization programs, LLR vaccine is relatively expensive for people in China. The low vaccination rate and the incomplete vaccination course made it difficult to evaluate the effect of whole course vaccination. Second, rRT-PCR is very sensitive for detecting rotavirus infection but does not correlate well with clinical disease. Enzyme immunoassay (EIA) tests was shown to correlate better with clinical disease. The estimates in this study might be an underestimate of the true VE due to using of rRT-PCR compared with EIA. Third, the number of laboratory-confirmed rotavirus infections was not sufficient to demonstrate the cross-protection against rotavirus gastroenteritis caused by serotypes other than G9. Moreover, the results of some subgroup analyses require to be confirmed by larger sample size study. Fourth, G10P[12] rotavirus shared relatively low identity in the nucleotide and amino acid sequences with the dominant strains of G9P[8]. Although LLR vaccine could induce neutralizing antibody responses in 40–60% of patients [23], we didn't evaluate the neutralizing antibody titer of cross-protection against prevalent rotavirus.

In summary, though the LLR vaccine was animal sourced and characterized as G10P[12], it appeared to confer protection for 1 dose versus 0 dose against gastroenteristis caused by some rotavirus serotypes. Compared to the cases without vaccination, children who are vaccinated prefer to present less severe clinical forms of the disease.

Authors' contributions

JL carried out the study design, participated in the experiment, performed data analysis and drafted the manuscript. YZ, YY and ZL participated in the experimental, performed the data analysis and reviewed the manuscript. YG, YT and BL participated in the data collection, analysis and reviewed the manuscript. LJ and LC participated in the experiment and reviewed the manuscript. QW contributed to the study design and provided a final review of this manuscript. All authors read and approved the final manuscript.

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Conflict of interest

There are no conflicts of interest on behalf of any of the authors.

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