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Effectiveness of rotavirus vaccine in preventing severe gastroenteritis in young children according to socioeconomic status

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ABSTRACT

In 2011, the monovalent rotavirus vaccine was introduced into a universal immunization program in Quebec (Canada). This retrospective cohort study assessed vaccine effectiveness (VE) in preventing acute gastroenteritis (AGE) and rotavirus gastroenteritis (RVGE) hospitalizations among children <3 y living in the Quebec Eastern Townships region according to socioeconomic status (SES). Data were gathered from a tertiary hospital database paired with a regional immunization registry. Three cohorts of children were followed: (1) vaccinated children born in post-universal vaccination period (2011–2013, n = 5,033), (2) unvaccinated children born in post-universal vaccination period (n = 1,239), and (3) unvaccinated children born in pre-universal vaccination period (2008–2010, n = 6,436). In each cohort, AGE and RVGE hospitalizations were identified during equivalent follow-up periods to calculate VE globally and according to neighborhood-level SES. Using multivariable logistic regression, adjusted odds ratios (OR) were computed to obtain VE (1-OR). Adjusted VE of 2 doses was 62% (95% confidence interval [CI]: 37%–77%) and 94% (95%CI: 52%–99%) in preventing AGE and RVGE hospitalization, respectively. Stratified analyses according to SES showed that children living in neighborhoods with higher rates of low-income families had significantly lower VE against AGE hospitalizations compared to neighborhoods with lower rates of low-income families (30% vs. 78%, p = 0.027). Our results suggest that the rotavirus vaccine is highly effective in preventing severe gastroenteritis in young children, particularly among the most well-off. SES seems to influence rotavirus VE, even in a high-income country like Canada. Further studies are needed to determine factors related to lower rotavirus VE among socioeconomically disadvantaged groups.

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Introduction

Rotavirus is the main cause of severe acute gastroenteritis (AGE) among children under 5 y of age worldwide.[1] In developed countries, severe rotavirus infections are usually not fatal but may result in hospitalizations, generating important costs for society.[2] Before the arrival of rotavirus vaccines in Canada, there were on average 7,500 to 10,500 estimated hospitalizations for rotavirus gastroenteritis (RVGE) annually.[3,4] Rotavirus infections were responsible for up to 72% of AGE hospitalizations during winter months.[5]

Two rotavirus vaccines, the pentavalent vaccine *RotaTeq*® (RV5; trademark of Merck & Co., Inc.) and the monovalent vaccine *Rotarix*® (RV1; trademark of the GlaxoSmithKline group of compagnies), were approved in Canada in 2006 and 2007 to prevent RVGE in young children.[6] Experimental studies showed high clinical efficacy of both vaccines in upper-middle and high-income countries, reducing RVGE hospitalizations by 85 to 100%.[7-9] On November 1st 2011, RV1 was introduced into a publicly-funded vaccination program in Quebec (Canada) with the aim to increase rotavirus vaccination and ultimately to reduce gastroenteritis morbidity in the general population, including vulnerable subgroups. RV1 is offered to all infants in 2 doses, administered orally, given at 2 and 4 months of age. Before its introduction into the universal immunization program, rotavirus vaccine coverage was low in Quebec as only 13.6% of children aged 1 y old were vaccinated on January 1st 2012.[10] Following its introduction in 2011, vaccine coverage rapidly increased to reach 85.9% in 2014.

This immunization program has proved to be as effective as other rotavirus vaccination programs in other industrialized countries; a descriptive study noting a 43% reduction of AGE hospitalization rates in children aged less than 5 y in 3 post-universal vaccination years (2011/2012–2013/2014) versus pre-universal vaccination years (2004/2005–2010/2011).[11] Cohort and case-control studies are however essential to estimate vaccine effectiveness (VE) at an individual-level and to better assess the potential of immunization in "real world" clinical practice. Such observational studies were conducted in many industrialized countries and found similar VE (88 to 100%) as pre-licensure clinical studies.[12-20] However, in low-income countries, lower VE was observed (46–57%).[21,22] To our knowledge, only one study has examined VE according to

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socioeconomic status (SES) using the SES rank of place of residence at the neighborhood level. This study, conducted in Israel, observed a significantly lower VE in preventing AGE in children of low-medium SES relative to higher SES (34% vs. 55%).[23] In a Canadian context where people benefit from the universal health care system and a publicly funded immunization program, VE stratified according to SES would be particularly useful to validate the effectiveness of the rotavirus vaccine in each socioeconomic subgroups of the population.

The aim of the present study was to assess VE of rotavirus vaccine (RVV) in children aged less than 3 y living in Eastern Townships (Quebec, Canada), globally and according to neighborhood-level SES.

Results

Study population

Unvaccinated children from post- and pre-universal vaccination cohorts were similar to vaccinated children with respect to various sociodemographic and health characteristics (Table 1). Follow-up time of unvaccinated children from post-universal vaccination period was longer when compared to the vaccinated cohort. As for other individual- and DA-level variables, unvaccinated and vaccinated cohorts were comparable although small differences reached the significance level for some characteristics.

VE

When using unvaccinated children from post-universal vaccination period as the "unexposed" group, VE for ≥1 dose was low and non-significant, preventing AGE and RVGE hospitalization by 23% (95% CI: −58%−63%) and 51% (95% CI: −443%−96%), respectively (Table 2). The proportions of hospitalized children were relatively close in the 2 cohorts, as 0.56% of vaccinated children were hospitalized for AGE during the study period compared to 0.89% for unvaccinated ones. With 2 doses, the RVV had a higher but still non-significant effectiveness, with VE of 41% (95% CI: −27%−73%) and 74% (95% CI: −316%−98%) to prevent AGE and RVGE hospitalizations, respectively.

For the unvaccinated cohort from pre-universal vaccination period, a greater proportion of children were hospitalized for AGE (1.35%) (Table 3). Using this cohort as the "unexposed" group, VE was particularly higher and significant. A partial or complete series of rotavirus vaccine was significantly effective, with VE of 58% (95% CI: 35%−72%) and 89% (95% CI: 55%−98%) to prevent AGE and RVGE hospitalizations, respectively, while VE for a complete series was 62% (95% CI: 37%−77%) and 94% (95% CI: 52%−99%) against AGE and RVGE hospitalizations, respectively.

VE according to socioeconomic characteristics

Stratified analyzes according to SES showed lower and non-significant VE against AGE hospitalization in most deprived subgroups (T3) as measured with rates of low-income families, unemployment and single mothers (Table 4). This observation was particularly true for the analysis based on low-income family rates, as children from disadvantaged neighborhoods (T3) had a twice lower VE (30% [95%

Table 1. Comparison of individual and neighborhood characteristics for the 3 cohorts (vaccinated children and unvaccinated children from pre- and post-universal vaccination periods).

	Vaccinated[a] cohort from **post**-universal vaccination period (n = 5,033)	Unvaccinated cohort from **pre**-universal vaccination period (n = 6,436)	p^b	Unvaccinated cohort from **post**-universal vaccination period (n = 1,239)	p^b
Sex, n (%)					
Male	2,588 (51.4)	3,304 (51.3)	0.927	646 (52.1)	0.655
Follow-up time, median [IR], months	16 [9–23]	16 [9–23]	**<0.001**	20 [11–29]	**<0.001**
Maternal age at birth, mean ± SD, years	28.7 ± 5.0	28.3 ± 5.0	**<0.001**	29.3 ± 4.8	**<0.001**
Prematurity, n (%)	405 (8.0)	475 (7.4)	0.183	117 (9.4)	0.111
Low birth weight, n (%)	311 (6.2)	384 (6.0)	0.636	101 (8.2)	**0.012**
Place of residence at birth, n (%)					
East	1,031 (20.5)	1,390 (21.6)	**0.025**	303 (24.5)	**0.006**
Central (Sherbrooke)	3,058 (60.8)	3,750 (58.3)		702 (56.7)	
West	944 (18.8)	1,296 (20.1)		234 (18.9)	
Low-income family rate, n (%)	3,320 (67.5)	4,296 (67.2)	0.691	807 (66.1)	0.342
T1 and T2 (low and middle)	1,597 (32.5)	2,100 (32.8)		414 (33.9)	
T3 (high)					
Unemployment rate, n (%)	3,317 (67.2)	4,236 (65.9)	0.151	819 (67.0)	0.869
T1 and T2 (low and middle)					
T3 (high)	1,618 (32.8)	2,189 (34.1)		404 (33.0)	
Single mothers rate, n (%)					
T1 and T2 (low and middle)	3,338 (67.5)	4,224 (65.6)	**0.037**	827 (67.5)	0.982
T3 (high)	1,608 (32.5)	2,212 (34.4)		399 (32.5)	
Proportion of mothers without high school diploma, n (%)					
T1 and T2 (low and middle)	3,380 (68.3)	4,227 (65.7)	**0.003**	824 (67.2)	0.448
T3 (high)	1,566 (31.7)	2,209 (34.3)		402 (32.8)	

[a]Vaccinated children received ≥1 dose of RVV before June 1st 2014.
[b]For comparison of vaccinated cohort and respective unvaccinated cohorts.
IR indicates interquartile range.
SD indicates standard deviation.

Table 2. Rotavirus VE for ≥1 and 2 doses in preventing hospitalization due to AGE and RVGE in vaccinated children compared to unvaccinated children from the post-universal vaccination period.

	Hospitalized	Total	Proportion (%)	Crude VE [95% CI], %	Adjusted VE[a] [95% CI], %
≥1 dose					
AGE					
Vaccinated	28	5,033	0.56		
Unvaccinated	11	1,239	0.89	38 [−26 to 69]	23 [−58 to 63]
RVGE					
Vaccinated	2	5,033	0.04		
Unvaccinated	1	1,239	0.08	51 [−443 to 96]	NA[b]
2 doses					
AGE					
Vaccinated	20	4,767	0.42		
Unvaccinated	11	1,239	0.89	53 [2 to 78]	41 [−27 to 73]
RVGE					
Vaccinated	1	4,767	0.02		
Unvaccinated	1	1,239	0.08	74 [−316 to 98]	NA[b]

[a]Adjusted for sex, maternal age at birth, prematurity and age at the end of the study in months.
[b]Multivariate analyses could not be performed because of the small number of cases in post-program period.
NA indicates non applicable.

CI: −40%−65%]) than those living in less deprived neighborhoods (T1 and T2), who had a VE of 78% (95% CI: 52%−89%) (p = 0.027). For children living in neighborhoods with higher rates of unemployment and single mothers, VE was also lower but not significantly different from other socioeconomic subgroups. On the other hand, children living in neighborhoods with a high proportion of low-educated mothers had higher VE than others, although these differences did not reach significance level. Although the evidence of heterogeneity of effect across SES strata may appear weak, these results remain intriguing and call for further research.

Discussion

This three-year retrospective cohort study assessed rotavirus VE to prevent AGE and RVGE hospitalizations, using both unvaccinated cohorts from pre- and post-universal vaccination periods as the "unexposed" group. Compared to unvaccinated children from the pre-universal vaccination period, VE for a complete series reached 62% and 94% against AGE and RVGE hospitalizations, respectively. Compared to unvaccinated children from the post-universal vaccination period, VE was low (41% and 74%, respectively). This is expected to be caused by the indirect protection of unvaccinated children documented in several post-licensure studies.[13,24,25] Although an unvaccinated cohort from post-universal vaccination period is generally preferred to calculate VE, our findings support the use of an unvaccinated cohort from pre-universal vaccination period to calculate VE because the high vaccine coverage of children in the post-universal vaccination period resulted in a considerable herd immunity effect. High vaccine coverage rates are expected to increase protection against rotavirus among vaccinated children but also among unvaccinated children by the reduced viral transmission of rotavirus in the community and the virus shedding from vaccinated children.[26]

Unvaccinated children from post-universal vaccination period were different from vaccinated children with respect to the follow-up time, unvaccinated children being followed on average for a longer period. Compared to vaccinated children, they were also more likely to be born in 2011, either because

Table 3. Rotavirus VE for ≥1 and 2 doses in preventing hospitalization due to AGE and RVGE in vaccinated children compared to unvaccinated children from the pre-universal vaccination period.

	Hospitalized	Total	Proportion (%)	Crude VE [95% CI], %	Adjusted VE[a] [95% CI], %
≥1 dose					
AGE					
Vaccinated	28	5,033	0.56		
Unvaccinated	87	6,436	1.35	59 [37 to 73]	58 [35 to 72]
RVGE					
Vaccinated	2	5,033	0.04		
Unvaccinated	24	6,436	0.37	89 [55 to 98]	NA[b]
2 doses					
AGE					
Vaccinated	20	4,767	0.42		
Unvaccinated	73	6,436	1.13	63 [40 to 78]	62 [37 to 77]
RVGE					
Vaccinated	1	4,767	0.02		
Unvaccinated	21	6,436	0.33	94 [52 to 99]	NA[b]

[a]Adjusted for sex, maternal age at birth, prematurity and age at the end of the study in months.
[b]Multivariate analyses could not be performed because of the small number of cases in post-program period.
NA indicates non applicable.

Table 4. Rotavirus VE for 2 doses in preventing hospitalization due to AGE in vaccinated children compared to unvaccinated children from the pre-universal vaccination period according to several socioeconomic characteristics.

	Hospitalized	Total	Proportion (%)	Crude VE[a] [95% CI], %	p[b]
Low-income family rate					
T1 and T2 (low and middle)					
Vaccinated	8	3,153	0.25		
Unvaccinated	48	4,296	1.12	78 [52 to 89]	
T3 (high)					**0.027**
Vaccinated	12	1,501	0.80		
Unvaccinated	24	2,100	1.14	30 [−40 to 65]	
Unemployment rate					
T1 and T2 (low and middle)					
Vaccinated	11	3,143	0.35		
Unvaccinated	48	4,236	1.13	69 [41 to 84]	
T3 (high)					0.279
Vaccinated	9	1,529	0.59		
Unvaccinated	24	2,189	1.10	47 [−15 to 75]	
Single mothers rate					
T1 and T2 (low and middle)					
Vaccinated	11	3,169	0.35		
Unvaccinated	46	4,224	1.09	68 [39 to 84]	
T3 (high)					0.404
Vaccinated	9	1,513	0.59		
Unvaccinated	27	2,212	1.22	52 [−3 to 77]	
Proportion of mothers without high school diploma					
T1 and T2 (low and middle)					
Vaccinated	15	3,217	0.47		
Unvaccinated	45	4,227	1.06	57 [22 to 76]	
T3 (high)					0.388
Vaccinated	5	1,465	0.34		
Unvaccinated	28	2,209	1.27	73 [31 to 90]	

[a]Multivariate analyses could not be performed because of the small number of cases in vaccinated children.
[b]Breslow-Day test used.

immunization program was not fully implemented during the first few months or because parents had a lower acceptability about the new recommended vaccine, which explains the longer follow-up time in this cohort. Sensitivity analysis comparing vaccinated and unvaccinated children born between January 2012 (rather than August 2011) and December 2013 showed similar VE results, suggesting that longer follow-up time in unvaccinated cohort did not affect results.

Our estimated VE for a complete series in preventing severe RVGE is similar to that observed in a recent case-control study from Quebec.[27] VE derived from our study is also consistent to that observed in other post-licensure field studies conducted in United States,[12-16] Australia,[17] France,[18] Finland[19] and Belgium,[20] where effectiveness of 88% to 100% was found. With respect to AGE hospitalizations, our result of 63% effectiveness is also similar to that found in previous retrospective cohort studies (53% to 62%).[12,13,17]

In the present study, children living in neighborhoods with the highest rates of low-income families, unemployed persons, and single mothers had lower VE against AGE hospitalization than their most well-off counterparts. However, statistically significant differences were only found when using low-income family rate as a SES proxy. Despite a small number of cases, the same differential effectiveness according to SES was observed for RVGE hospitalizations (data not shown). Our findings are consistent with a study conducted in Israel that observed lower VE to prevent AGE in children living in middle-low socioeconomic areas.[23] Our results suggest that other factors than vaccination could influence either the exposure to the infectious agent, the susceptibility to this agent, or the medical care following disease (i.e. diagnosis and hospitalization). Indeed, residents from deprived areas may have different hygiene behaviors, health conditions and health seeking behavior than the general population. Poor nutritional status, weakened immune system or house crowding could further increase the risk of viral transmission and/or impair the development of a robust immune response following immunization, as suggested elsewhere.[31] Moreover, low SES parents may be less knowledgeable about the causes and cures of symptoms,[32] making them less likely to provide appropriate care at home. This may prompt physicians to pre-emptively hospitalize children with gastroenteritis from deprived families. In the province of Quebec, this practice was previously observed among asthmatic children, as those whose fathers held economically-disadvantaged occupations were more likely to be hospitalized.[33] Health characteristics of people from disadvantaged neighborhood and differential management from physicians regarding the family SES may thus explain the higher hospitalization rates and consequently, the lower rotavirus VE against AGE hospitalization observed among disadvantaged children. Indeed, 3 of the 4 socioeconomic characteristics examined showed low and non-significant VE among disadvantaged children. However, we had sufficient statistical power to detect difference in VE between subgroups for only one of these characteristics. Thus, these findings should be interpreted with caution and be considered as hypothesis-generating. Additional studies conducted in other settings are thus required, preferably using individual-level SES.

An important strength of this cohort study was the assessment of VE over 3 consecutive post-universal vaccination years to take into account natural year-to-year variations of rotavirus

activity.[18,34] In a context of high vaccine uptake since the implementation of the rotavirus program, selection of a similar cohort of children from pre-universal vaccination period was highly relevant to calculate an unbiased VE. In addition, this retrospective analysis of 2 regional databases was made on the entire pediatric population born at the CHUS and living in the Eastern Townships, allowing for a potential generalizability of results to the province of Quebec.

Besides the strengths, there were several limitations. The unvaccinated cohort from pre-universal vaccination period used as comparison group to calculate VE might not had been exposed to the same infectious risk of the virus compared to the vaccinated cohort from post-universal vaccination period. However, children from these 2 cohorts had a similar follow-up time and allowed to calculate a VE not affected by the strong herd immunity effect of the vaccine. Because laboratory testing for rotavirus is not routinely performed for all children with gastroenteritis, true burden of RVGE hospitalizations may be underestimated.[35,36] However, laboratory testing practices were similar over the 6-year study period, as the proportion of requests among hospitalized children was equivalent in pre- and post-universal vaccination periods (data not shown). Regarding CIRESSS and LOGIVAC, both databases had no information about whether a child had moved out of the Eastern Townships since birth. This loss to follow-up has the potential effect of underestimating the occurrence of gastroenteritis hospitalizations and might lead to outcome misclassification. However, this bias is presumably non-differential between vaccinated and unvaccinated children. Moreover, both databases did not provide any information on some potentially confounding variables such as daycare attendance and individual-level SES. However, several proxies of the SES of parents were used and were measured at the finest ecological level available.

Methods

Study setting

The Eastern Townships (320,008 residents in 2014) is a southern region of Quebec composed of a mix of urban, semi-urban, and rural communities.[37] The central city, Sherbrooke (Quebec's 6th largest), has half of the regional population (162,638 residents in 2014). This city contains one central hospital, the *Centre hospitalier universitaire de Sherbrooke* (CHUS), where 95% of deliveries in the Eastern Townships are performed and where nearly 100% of pediatric beds for acute care in the region are held.[4] Therefore, the vast majority of children living in Eastern Townships requiring hospitalization for AGE attend the CHUS.

Data sources

CIRESSS (*Centre informatisé de recherche évaluative en services et soins de santé*) is a local data warehouse based at the CHUS. It contains exhaustive data on all births and hospitalizations performed at the CHUS since 1991. LOGIVAC is a comprehensive immunization registry that records all childhood vaccines administered to residents of the Eastern Townships since the early 1990s. It provides information about rotavirus vaccines, including name, date of administration and number of doses received. Newborn registrations in this database are made from the notice of live births in the region. Thus, all children born in the Eastern Townships, regardless of their vaccination status, are included in LOGIVAC. In a previous descriptive study, these 2 databases were paired to examine gastroenteritis hospitalization rates and vaccination status among a large cohort of children born between June 1999 and May 2014 in pre- and post-universal vaccination periods.[11] The same database was used to assess VE in the present study.

Study population

This retrospective cohort study included 3 cohorts of children born at the CHUS and living in the Eastern Townships at birth: (1) vaccinated children who received 1 or 2 doses of RV1 born between August 1st 2011 and December 31st 2013 (n = 5,033), (2) unvaccinated children born in post-universal vaccination period (between August 1st 2011 and December 31st 2013, n = 1,239), and (3) unvaccinated children born in pre-universal vaccination period (between August 1st 2008 and December 31st 2010, n = 6,436). Five children with mixed series (RV1 and RV5) and 14 children with 3 doses of RV1 were excluded from the first cohort. All newborns included in the first 2 cohorts were age-eligible to receive a complete series of the rotavirus vaccine free of charge from November 1st 2011 until the end of the study in May 31st 2014. They were followed up until the end of the study (mean follow-up of 16 months and maximum observational period of 31 months) while newborns in the pre-universal vaccination cohort were followed-up over an equivalent period, until May 31st 2011. A pre-universal vaccination cohort of unvaccinated children was selected, as pre-universal vaccination years had very low vaccine coverage (1%), precluding herd immunity among unvaccinated children. Indeed, indirect protection among unvaccinated children from post-universal vaccination period could lead to potential underestimation of the VE.

Variables

Exposure

Using data provided by LOGIVAC, 2 independent dichotomous variables were used to determine vaccination status: (1) partial or complete series (1 or 2 doses) vs. 0 dose of RVV and (2) complete series (2 doses) versus 0 dose of RVV.

Outcomes

The two dependant variables studied were the occurrence of AGE hospitalization and RVGE hospitalization (yes vs. no). Hospitalizations for AGE, a proxy for severe AGE, were retrospectively identified in CIRESSS using the following *International Classification of Diseases, 9th Revision and 10th Revision, Canada* (ICD-9/10-CA) codes: AGE of determined etiology (bacterial [003.0, 004, 005, 008.0–008.5/A02.0, A03–A05], parasitic [006.0–006.1, 007/A06.0–A06.3, A07], and viral [008.6–008.8/A08, including rotavirus code 008.61/A08.0]), AGE of undetermined etiology (presumed infectious [009/A09] and presumed noninfectious [558.4–558.9/K52.8–K52.9]) and

noninfective neonatal AGE [P78.3]. Using laboratory data in CIRESSS, hospitalizations for RVGE were considered if stool analysis was rotavirus-positive.

Follow-up of vaccinated children with ≥1 dose began 14 d after the first dose was administered while follow-up of vaccinated children with 2 doses started 14 d after the second dose was administered. Thus, if a hospitalization for AGE or RVGE occurred between the first and second dose, it was only considered for VE calculation of ≥1 dose. A two-week delay was also used in previous randomized clinical trials to provide sufficient time to establish a fully developed vaccine immune response.[7] For unvaccinated children, follow-up began 14 d following the recommended ages for receiving the first and second doses, i.e., 75 d (2 months and 14 days) and 136 d (4 months and 14 days). Follow-up ended when the child was hospitalized for an AGE or RVGE, or at the end of the study on May 31st 2014 or May 31st 2011 for the post- and pre-universal vaccination cohorts, respectively.

Covariates

Several potential confounders were available in the CIRESSS database. Birthdate was used to calculate age at the end of the study (in months) for each birth cohorts, and quarter of birth. Sex, maternal age at birth, prematurity (i.e. <37 weeks of gestation) and low birth weight (<2,500 g) were also extracted. Place of residence, defined as Eastern, Central (i.e., Sherbrooke city) and Western areas, was determined by the municipality of residence at birth.

Socioeconomic characteristics

The rate of low-income families (i.e. families having an annual income below the low-income cut-off[38]), the unemployment rate among persons ≥25 years of age, the rate of single mothers (i.e., not living with a partner) and the proportion of mothers without a high school diploma (i.e. <11 school years completed), derived from the National Census (2006) and the Live Births File (2002–2010) data, were measured at dissemination area (DA)-level. DA is the smallest geostatistical unit available from the census (approximately 400 to 700 persons by DA).[39] The 6-digit residential postal codes at birth, provided by CIRESSS, were geocoded in order to assign a DA to each participant (total of 512 DA). These ecological variables were then categorized in tertiles (T1, T2, T3), T3 representing the highest rate or proportion of poor socioeconomic indicators. In the absence of individual measures, these neighborhood-level variables were used as proxy measures for the SES of participants.

Statistical analyses

Differences between the 3 cohorts (vaccinated children, unvaccinated children from post-universal vaccination period and unvaccinated children from pre-universal vaccination period) were assessed using χ^2-test for categorical variables and Student's *t*-test for continuous variables, with significance level set at 0.05 (2-sided). VE, presented as a percentage with a 95% confidence interval (CI), was obtained by the following formula: (1- odds ratio [OR]) x 100, OR being the estimated relative risk of AGE or RVGE hospitalization in the vaccinated group compared with that in the non-vaccinated group. All potentially confounding variables associated with either outcome or exposure at $p < 0.2$ were then introduced into a multivariable logistic regression model to obtain adjusted VE. The least statistically significant variables were excluded one by one from the model to obtain the final multivariable model. VE to prevent RVGE hospitalization was not adjusted due to the small number of cases in post-universal vaccination period. Moreover, VE was also stratified according to neighborhood-level SES. The Breslow-Day test was used to compare VE between different strata, also with a significance level set to 0.05. Stratified VE were not adjusted because of the small number of cases. Data were analyzed using SPSS. The research project was approved by the CHUS Ethics Committee.

Conclusions

This study confirms the effectiveness of RVV among children during the first 3 post-universal vaccination years, in a high-coverage, developed country setting. However, RVV appears to be less effective in preventing severe gastroenteritis among the most disadvantaged subgroups. Further studies are required to determine factors related to low SES which may influence rotavirus VE.

Abbreviations

AGE	acute gastroenteritis
CHUS	*Centre hospitalier universitaire de* Sherbrooke
CI	confidence interval
DA	dissemination area
ICD-9/10-CA	International Classification of Diseases 9th Revision and 10th Revision, Canada
RR	relative risk
RV1	monovalent rotavirus vaccine
RV5	pentavalent rotavirus vaccine
RVV	rotavirus vaccine
RVGE	rotavirus gastroenteritis
SES	socioeconomic status
T1	first tertile
T2	second tertile
T3	third tertile
VE	vaccine effectiveness

Disclosure of potential conflicts of interest

The authors have no conflict of interest to disclose.

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