International Journal of Infectious Diseases 105 (2021) 277–285

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Rotavirus genotype trends from 2013 to 2018 and vaccine effectiveness in southern Vietnam

Dung Thi Thuy Truong[a,b,†], Ji-Man Kang[c,d,†], Ngoc Thi Hong Tran[e,†], Lan Trong Phan[g], Hung Thanh Nguyen[f], Thang Vinh Ho[a], Thao Thi Thanh Nguyen[h], Phuc Le Hoang[e], Trang Mai Thuy Pham[h], Thuy Dieu Nguyen[a], Thang Anh Hoang[a], Quang Chan Luong[a], Quang Duy Pham[i,j], Jong Gyun Ahn[c,d], Sangchul Yoon[l], Thuong Vu Nguyen[g,**], Joon-Sup Yeom[k,*]

[a] Department for Disease Control and Prevention, Pasteur Institute, Ho Chi Minh City, Vietnam
[b] Department of Global Health Security, Graduate School of Public Health, Yonsei University, Seoul, South Korea
[c] Department of Paediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, South Korea
[d] Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, South Korea
[e] Department of Gastroenterology, Children's Hospital 1, Ho Chi Minh City, Vietnam
[f] Directorial Board, Children's Hospital 1, Ho Chi Minh City, Vietnam
[g] Directorial Board, Pasteur Institute, Ho Chi Minh City, Vietnam
[h] Microbiology and Immunology Department, Pasteur Institute, Ho Chi Minh City, Vietnam
[i] Planning Division, Pasteur Institute, Ho Chi Minh City, Vietnam
[j] Training Centre, Pasteur Institute, Ho Chi Minh City, Vietnam
[k] Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea
[l] Department of Medical Humanities and Social Sciences, College of Medicine, Yonsei University, Seoul, South Korea

ARTICLE INFO

Article history:
Received 20 December 2020
Received in revised form 9 February 2021
Accepted 10 February 2021

Keywords:
Rotavirus
Genotype
Vaccine
Vaccine effectiveness
Rotarix
Surveillance
Vietnam

ABSTRACT

Objectives: Rotavirus (RV) genotypes vary geographically, and this can affect vaccine effectiveness (VE). This study investigated the genotype distribution of RV and explored VE before introducing the RV vaccine to the national immunization programme in Vietnam.

Methods: This hospital-based surveillance study was conducted at Children's Hospital 1, Ho Chi Minh City in 2013–2018. Stool samples and relevant data, including vaccination history, were collected from children aged <5 years who were hospitalized with gastroenteritis. RV was detected using enzyme immunoassays and then genotyped. Children aged ≥6 months were included in the VE analysis.

Results: Overall, 5176 children were included in this study. RV was detected in 2421 children (46.8%). RV positivity decreased over the study period and was associated with age, seasonality, location and previous vaccination. Among 1105 RV-positive samples, G3P[8] was the most prevalent genotype (43.1%), followed by G8P[8] (19.7%), G1P[8] (12.9%) and G2P[4] (12.9%). Overall VE was 69.7% [95% confidence interval (CI) 53.3–80.6%] in fully vaccinated children and 58.6% (95% CI 44.1–69.4%) in children who had received at least one dose of RV vaccine. VE was highest for G3P[8] (95% CI 75.1–84.5%) and lowest for G2P[4] (95% CI 32.4–57.2%).

Conclusions: RV remains a major cause of acute gastroenteritis requiring hospitalization in southern Vietnam. The RV vaccine is effective, but its effectiveness varies with RV genotype.

Background

Despite incidence rates decreasing worldwide, rotavirus (RV) infection remains the leading cause of severe dehydrating diarrhoea in infants and young children (Kotloff et al., 2013; World Health Organization, 2013b; GBD Mortality and Causes of Death Collaborators, 2015; GBD 2013 Mortality and Causes of Death Collaborators, 2015; Tate et al., 2016). Worldwide estimates

* Corresponding author at: Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea.
** Corresponding author at: Pasteur Institute in Ho Chi Minh City, 167 Pasteur Street, District 3, Ho Chi Minh City 724000, Vietnam.
E-mail addresses: nguyenthuong@yahoo.com (T.V. Nguyen), joonsup.yeom@yuhs.ac (J.-S. Yeom).
† Contributed equally to this manuscript.

https://doi.org/10.1016/j.ijid.2021.02.047

suggest that 258.2 million children aged <5 years suffered from severe RV gastroenteritis (RVGE) in 2018. This disease causes an estimated 0.1 million RV-related deaths annually, the majority of which occur in low- and middle-income countries (LMICs) (GBD 2016 Diarrhoeal Disease Collaborators, 2018).

Vaccination is one of the best strategies for reducing RV-associated morbidity and mortality. Despite the recommendation by the World Health Organization (WHO) to introduce RV vaccination with a goal of 90% vaccine coverage in all countries, and financial support from the Global Alliance for Vaccines and Immunization to 45 countries, the global coverage was still low at 39% in 108 countries at the end of 2019 (World Health Organization, 2013a, 2020).

RV infection is a significant burden in Vietnam. In a cohort study of children aged <5 years conducted in 2002 and 2003, an estimated 820,000 outpatient consultations and 122,000–140,000 hospitalizations occurred annually, representing one of the highest numbers of cases of hospitalization due to RVGE in South-east Asia (Anh et al., 2006). Furthermore, approximately 5500 children are estimated to die of RVGE annually; the mortality rate is 3.6 per 1000 per year, accounting for 4.3–8.5% of all deaths in children aged <5 years (Van Man et al., 2001). The annual economic burden is estimated to be US$3.8 million in direct costs and US$1.5 million in indirect costs (Fischer et al., 2005). Despite the heavy burden of RV infection, RV vaccination was not included in the national immunization programme (NIP) in Vietnam until December 2019.

Two WHO-prequalified vaccines and one locally licensed vaccine are used in Vietnam. Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium), RotaTeq (Merck and Co., Durham, NC, USA), and the locally licensed Rotavin-M1 (Polyvac, Nha Trang City, Vietnam) are based on the G1P[8] strain and have efficacy similar to that of Rotarix (Folorunso and Sebolai, 2020). These RV vaccines are currently self-financed in Vietnam, and no data are available on RV vaccine coverage in the country. Vaccine effectiveness (VE) can be influenced by several factors, including age, geographic location, seasonality, nutrition status, breastfeeding, co-existing enteropathy, and RV genotype distribution (Trang et al., 2014; Tate et al., 2016; Folorunso and Sebolai, 2020). The RV genotype distribution fluctuates over time, and is based on the geographic area. It is often unpredictable. Moreover, some genotypes, such as G2P[4], G12P[8] and equine-like G3P[8], are associated with low VE (Ruiz-Palacios et al., 2006; Ali et al., 2016; Roczo-Farkas et al., 2018; Pietsch and Liebert, 2019; Folorunso and Sebolai, 2020). Therefore, long-term epidemiological data, including data on genotype distribution, are essential to establish an effective vaccine strategy (Roczo-Farkas et al., 2018; Folorunso and Sebolai, 2020). However, in Vietnam, genotype-specific VE according to G/P genotype has not been evaluated previously.

This study aimed to investigate RV genotype distribution among infants and young children hospitalized because of RVGE in southern Vietnam. In addition, the study explored other additional risk factors for severe RVGE and VE based on vaccination history..

Methods

Study design and surveillance system

This prospective hospital-based surveillance study was conducted from January 2013 to December 2018 at Children's Hospital 1, Ho Chi Minh City, one of the Vietnam Rotavirus Surveillance Network hospitals in Vietnam. This hospital-based network was established in 1998 and has published several country-specific reports (Supplementary Methods 1 and 2, see online supplementary material) (Van Man et al., 2001; Nguyen et al., 2004; Bodhidatta et al., 2007). Children aged <5 years whose primary reason for hospitalization was acute watery diarrhoea, defined as three or more loose stools within 24 h for <14 days, were included in this study. Children with bloody diarrhoea, acute diarrhoea acquired after admission, and those whose parents or guardians did not allow their child's enrolment were excluded from the study. The institutional review boards of the Children's Hospital 1 and Yonsei University approved the study.

Stool specimen collection, virus detection and genotype analysis

Stool specimens were obtained from each child within 48 h of admission for laboratory confirmation of RV. Specimens were stored at −20 °C and then sent to the Pasteur Institute, located approximately 3 km from the hospital. Specimens were tested for RV using a commercial enzyme immunoassay (EIA) ProSpecT (Oxoid, Basingstoke, UK). At least 25% of EIA-positive samples were selected at random, and used for P and G genotyping with a semi-nested multiplex reverse-transcriptase polymerase chain reaction using methods described previously (Nguyen et al., 2004).

Clinical data collection

Using a standard case definition and case-based data collection tool, the hospital staff prospectively identified children aged <5 years admitted to the hospital or emergency unit with acute diarrhoea. Enrolled children had received routine medical care provided by a paediatrician. Demographic data, medical history, RV vaccination history and clinical manifestations were recorded by questioning parents/caregivers or from the child's vaccination card. Information on the date of discharge, disease outcome and discharge diagnosis was abstracted from the children's medical charts. All information was recorded on the standardized case investigation form.

Severity index, seasonal/geographical distribution and general statistics

The severity of diarrhoea at admission was assessed using the Vesikari clinical severity scoring system (Supplementary Methods 3, see online supplementary material). Scores of >10 points, 7–10 points and <7 points indicated severe, moderate and mild diarrhoea, respectively. As records of fever were not available in 2013 and 2014, the Vesikari score was not calculated for children admitted in 2013 and 2014. A description of geographical divisions is provided in Supplementary Methods 4 (see online supplementary material). Seasons were divided into a dry season (November–April) and a rainy season (May–October) to emphasize seasonal trends. General statistical information regarding Vietnam, including population size, poverty rate, under-five mortality rate and monthly income per capita by province, was obtained from the General Statistical Office of Vietnam (www.gso.gov.vn) (Supplementary Table 1, see online supplementary material).

Vaccine effectiveness

Children were included in the VE analysis if they were aged ≥6 months at the time of admission. RotaTeq is recommended for routine oral administration for all infants as a three-dose series at 2, 4 and 6 months of age, and Rotarix and Rotavin-M1 are recommended as a two-dose series at 2 and 4 months of age. Cases in whom all doses were completed were defined as 'complete RV vaccination', and cases in whom all doses were not completed were defined as 'incomplete RV vaccination'. A dose was considered valid if the RV infection was notified >14 days after RV vaccine administration to allow time for the child to develop a protective

immune response. Two methods were used to analyse VE. In the first analysis, children with complete immunization were included in the vaccinee group and children with incomplete vaccination were included in the non-vaccinee group. In the second analysis, all children who had received at least one dose of vaccine were included in the vaccinee group and those who had not received any doses of vaccine were included in the non-vaccinee group. For both methods, VE against RVGE was calculated using the following formula: VE = (1−adjusted odds ratio [OR]) ×100 [%]).

Statistical analysis

Categorical variables were compared using Chi-squared test or Wilcoxon rank-sum test, and continuous variables with normal distributions were compared using the independent *t*-test. The linear-by-linear association test was used for year-trend analysis. Conditional logistic regression models were used to determine the odds ratio for VE calculations. Statistical analyses were performed using SAS Version 9.4 (SAS Inc., Cary, NC, USA), R Version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism Version 8.4.2 (GraphPad Software, La Jolla, CA, USA).

Results

Patients' characteristics

In total, 5254 children were enrolled over the study period, of whom 5176 were included in the analysis (Figure 1). In total, 2421 children (46.8%) had RVGE, based on stool specimen findings. The mean age at admission was 13.0 ± 8.4 months, and >78.8% of patients were aged between 6 and 23 months. There were no annual or seasonal differences in patient characteristics. Only 199 children (3.9%) had received at least one dose of RV vaccine prior to hospitalization, and 130 children (2.5%) were fully vaccinated. Of the children with RVGE, 38.1% had severe symptoms on admission and 9.2% required intravenous hydration. There was one fatal case of RVGE in 2017. Other patient characteristics are described in Table 1.

Characteristics and risk factors of rotavirus gastroenteritis

The RV-positive rate declined from 55.3% in 2013 to 43.5% in 2018 ($P < 0.001$, Figure 2A). The RV-positive rate increased with age, although the absolute number of children with RVGE was lower among children aged 24–59 months (Figure 2B). Children with RVGE manifested more severe symptoms than children with other forms of acute gastroenteritis (44.7% vs 32.8%; $P < 0.001$), and RVGE was more prevalent in the dry season than in the rainy season (62.3 vs 37.8%; $P < 0.001$; Table 1 and Figure 2C). RVGE hospitalization was lower in children who lived in the south-eastern region than in children who lived in the south-western region (Table 1). The RVGE hospitalization rate in 2018 and the major economic and sanitation indicators in the south-eastern and south-western regions are shown in Figure 2D.

On multi-variable logistic analysis, age ≥6 months, earlier year of hospitalization, dry season, residence other than the south-eastern region, and non-vaccination were identified as risk factors for RVGE requiring hospitalization (Table 2). Additionally, age ≥12 months, dry season, and non-vaccination or incomplete vaccination were risk factors for severe RVGE (Table 2).

Distribution of rotavirus genotypes

Of the RV-positive stool specimens, 1105 (45.6%) were sent for genotype analysis. G3 was the most prevalent G genotype (46.3%) and P[8] was the most prevalent P genotype (83.3%, Table 3). G3P[8] was the most prevalent G/P genotype, followed by G8P[8], G1P[8] and G2P[4]. There were major secular variations in genotype distribution over the study period. The prevalence of G1P[8] decreased sharply from 69.9% in 2013 to 0% in 2018, while the prevalence of G3P[8] increased from 8.1% in 2013 to a peak of 60.7% in 2017 and then decreased to 41.2% in 2018 (Figure 2E). The prevalence of G8P[8] increased from 0% in 2013 to a peak of 47.2% in 2016 and then decreased to 23.9% in 2018. The prevalence of G2P[4] increased from 15.5% in 2013 to 37.4% in 2014, decreased to 0.4% in 2016, and then increased to 16.3% in 2018 (Figure 2E).

G3P[8] was the most prevalent genotype in all age groups. There were minor differences in the prevalence of other genotypes

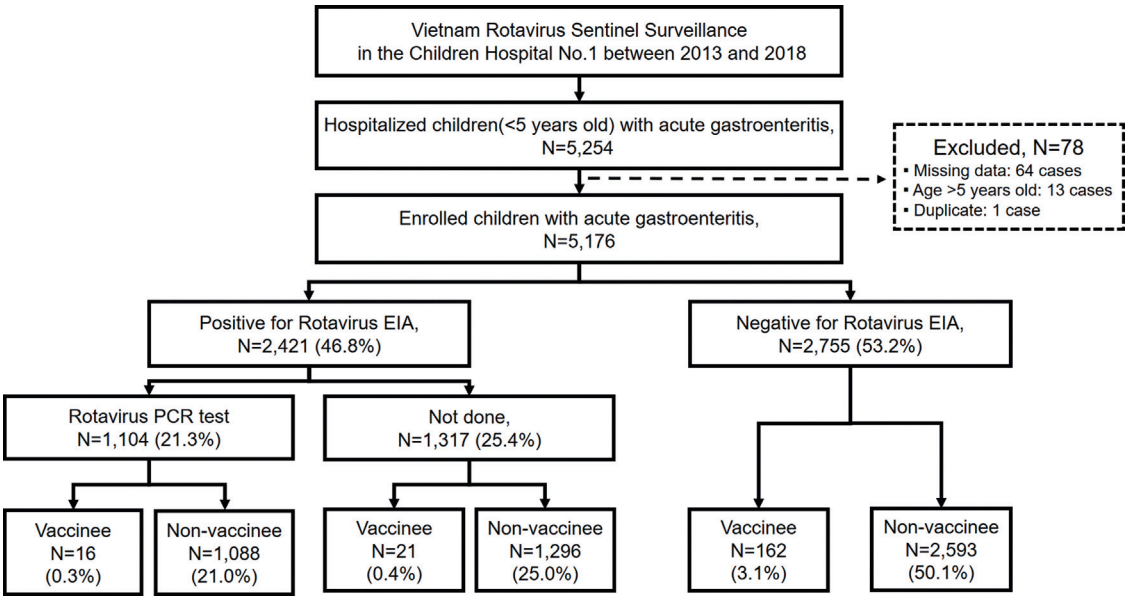


Figure 1. Flow chart for the enrolment of study patients.

Table 1
Characteristics of the study participants.

Characteristics	Total		RV-positive gastroenteritis		RV-negative gastroenteritis		*P*-value
	n	(%)	*n*	(%)	*n*	(%)	
Age in months, mean (SD)	5176	13.0 ± 8.4	2421	14.0 ± 8.5	2755	12.2 ± 8.3	<0.001
<6	572	11.1	178	7.4	394	14.3	<0.001
6–11	2169	41.9	940	38.8	1229	44.6	
12–23	1911	36.9	1016	42.0	895	32.5	
24–59	524	10.1	287	11.9	237	8.6	
Sex	5176		2421		2755		0.93
Male	3315	64.1	1552	64.1	1763	64.0	
Female	1861	36.0	869	35.9	992	36.0	
Admission year	5176		2421		2755		<0.001
2013	825	15.9	456	18.8	369	13.4	
2014	839	16.2	385	15.9	454	16.5	
2015	827	16.0	374	15.5	453	16.4	
2016	914	17.7	417	17.2	497	18.0	
2017	958	18.5	435	18.0	523	19.0	
2018	813	15.7	354	14.6	459	16.7	
Seasonality	5176		2421		2755		<0.001
Dry season (November–April)	2667	51.5	1521	62.8	1146	41.6	
Rainy season (May–October)	2509	48.5	900	37.2	1609	58.4	
Geographical distribution	5176		2421		2755		<0.001
South-eastern	2750	53.1	1210	50.0	1540	55.9	
South-western (Mekong River Delta)	1852	35.8	930	38.4	922	33.5	
Other	574	11.1	281	11.6	293	10.6	
RV vaccination before infection	5163		2415		2748		<0.001
Unvaccinated	4964	96.1	2378	98.5	2586	93.9	
RV vaccinated[a]	199	3.9	37	1.5	162	5.9	
Complete	130	2.5	18	0.7	112	4.1	
Incomplete	40	0.8	11	0.5	29	1.1	
Unknown[b]	29	0.6	8	0.3	21	0.8	
Vesikari score	3356		1509		1847		<0.001
<7 (mild)	972	29.0	386	25.6	586	31.7	
7–10 (moderate)	1104	32.9	448	29.7	656	35.5	
≥11 (severe)	1280	38.1	675	44.7	605	32.8	
Management							
ORS (n = 5156)[c]	5009	97.2	2350	97.4	2659	96.9	0.26
IV hydration (n = 5156)[c]	438	8.5	236	9.8	202	7.4	0.002
Antimicrobials (n = 5112)[c]	396	7.8	150	6.3	246	9.1	<0.001
Outcome							
Duration of hospitalization in days, mean (SD)	4986	4.5 ± 4.0	2327	4.3 ± 3.7	2659	4.6 ± 4.2	0.11

RV, rotavirus; ORS, oral rehydration solution; IV, intravenous; SD, standard deviation.
[a] Among them, 134 patients received Rotarix, 27 patients received RotaTeq, 10 patients received Rotavin-M1, and 28 patients received an unknown vaccine.
[b] Number of vaccinations had not been registered.
[c] Number of available data is indicated.

according to age, although these differences were not significant (Supplementary Table 2, see online supplementary material).

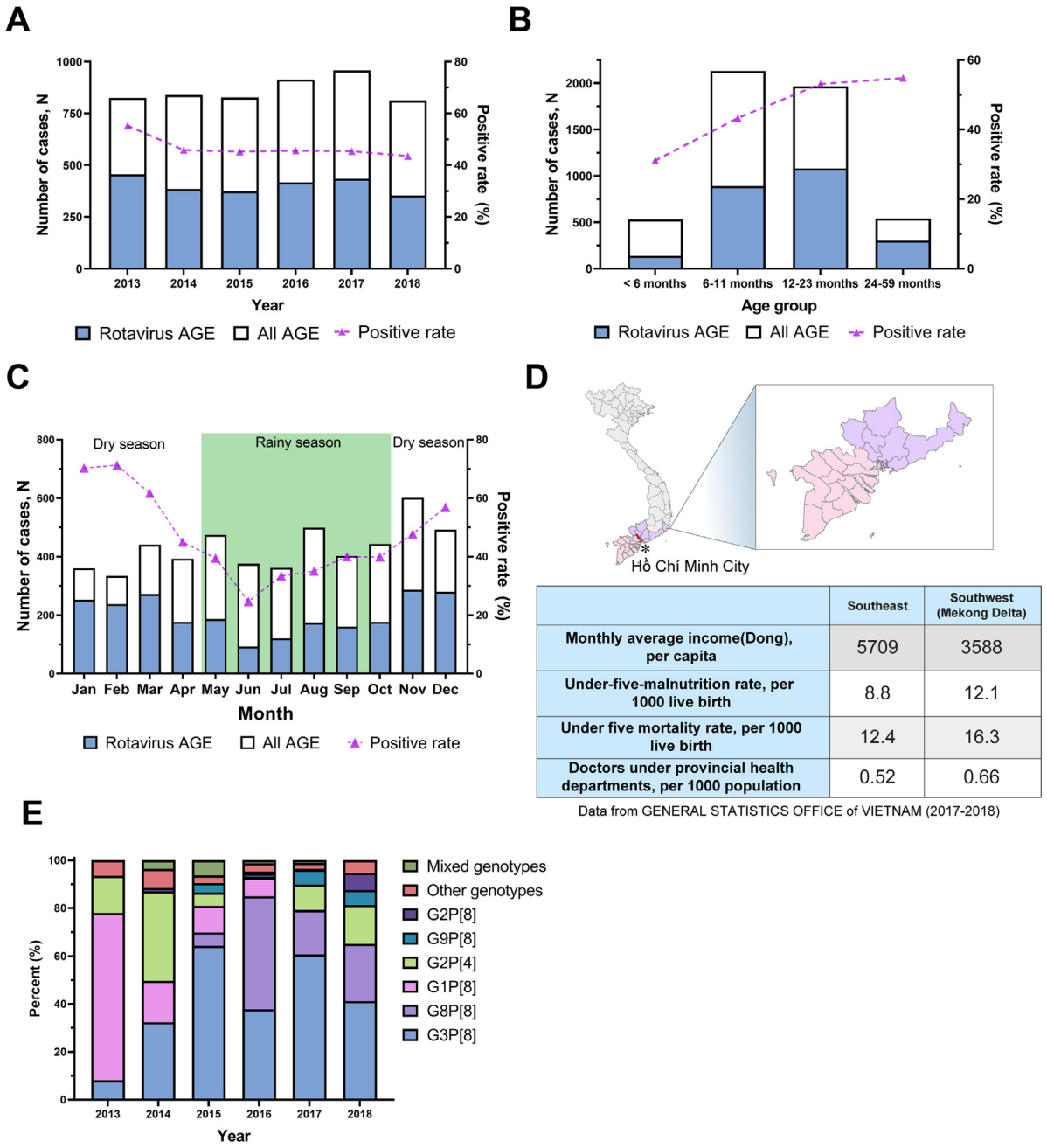
Rotavirus vaccine effectiveness

In total, 4593 children were age-eligible for VE analysis. VE was 69.7% [95% confidence interval (CI) 53.3–80.6%] among those who were fully vaccinated and 58.6% (95% CI 44.1–69.4%) among those who had received at least one dose of vaccine (Figure 3A,B). VE was highest among children aged 24–59 months (77.4% and 100% for those who had received at least one dose of vaccine and those who were fully vaccinated, respectively) and lowest among children aged 12–23 months (47.6% and 55.5% for those who had received at least one dose of vaccine and those who were fully vaccinated, respectively); however, the differences in VE by age were not significant. Among the 3383 children with genotyping data available, the VE values for a completed schedule were 84.5%, 76.3%, 67.1% and 57.2% for G3P[8], G1P[8], G8P[8] and G2P[4], respectively, and the VE values for having received at least one dose of vaccine were 75.1%, 49.3%, 38.0% and 32.4% for G3P[8], G1P[8], G8P[8] and G2P[4], respectively. However, as only a limited number of children (n = 104) had received one or more doses of RV vaccine, the differences in VE by genotype were not significant.

When VE analysis was restricted to Rotarix, the most commonly used vaccine (67.3%, 134/199), overall VE was 75.4% (95% CI 58.1–85.5%) for a completed schedule and 71.8% (95% CI 54.9–82.4%) for at least one dose of Rotarix (Figure 3C,D). In the analysis of Rotarix VE by genotype, the values for a completed schedule were 100%, 85.3%, 67.7% and 46.7% for G1P[8], G3P[8], G8P[8] and G2P[4], respectively, and those for having received at least one dose of Rotarix were 100%, 84.2%, 65.2% and 25.3% for G1P[8], G3P[8], G8P[8] and G2P[4], respectively. Further details on VE according to genotype are provided in Figure 3.

Discussion

This sentinel surveillance study showed the trends in RV infection in southern Vietnam from 2013 to 2018. Despite a declining trend, the burden of RV infection remained high. There was a major shift in the distribution of genotypes during the study period: the prevalence of G3P[8] increased and the prevalence of G1P[8] decreased. The overall VE of RV vaccines appeared high but VE varied according by genotype. Unlike previous studies that focused solely on genotyping and RV epidemiology, this study provides estimates of RV VE in Vietnam during a period when RV vaccination was self-financed (Nguyen et al., 2004; Bodhidatta et al., 2007; Trang et al., 2014; Huyen et al., 2018).



	Southeast	Southwest (Mekong Delta)
Monthly average income(Dong), per capita	5709	3588
Under-five-malnutrition rate, per 1000 live birth	8.8	12.1
Under five mortality rate, per 1000 live birth	12.4	16.3
Doctors under provincial health departments, per 1000 population	0.52	0.66

Data from GENERAL STATISTICS OFFICE of VIETNAM (2017-2018)

Figure 2. Characteristics of rotavirus gastroenteritis according to year, age, seasonality, geographic location and genotype. (A) Yearly trend of rotavirus gastroenteritis. Positivity decreased from 55.3% in 2013 to 43.5% in 2018 (asymptotic linear-by-linear association test: Z = 4.1, $P < 0.001$). (B) Proportions of rotavirus gastroenteritis and rotavirus positivity by age group. (C) Seasonality and monthly distribution of rotavirus gastroenteritis. Rotavirus gastroenteritis tended to be more prevalent in the dry season (November–April) than the rainy season (May–October) (positivity 62.3% vs 37.8%; $P < 0.001$). (D) Positivity of rotavirus gastroenteritis in 2018 and the major economic and sanitation indicators in south-west and south-east Vietnam. *Ho Chi Minh City, located in the south-eastern region. The south-eastern region had higher socio-economic status and better sanitation (higher GDP and lower under-5 mortality rates), and had lower rotavirus gastroenteritis rates than the south-western region, which had lower socio-economic status and poor sanitation. (E) Fluctuation in the distribution of rotavirus genotypes from 2013 to 2018. The prevalence of G1P[8] decreased sharply from 69.9% in 2013 to 0% in 2018, while G3P[8] became the most prevalent genotype from 2014 to 2018. Changes were also observed in the prevalence of G8P[8] and G2P[4]. AGE, acute gastroenteritis.

The positive rate of RVGE in this study (46.8%) was similar to that reported in Vietnam for 2012–2015 based on National Sentinel Surveillance data (46.7%) (Huyen et al., 2018). This rate was higher than rates reported from other Association of Southeast Asian Nations (ASEAN) countries, such as the Philippines (38.1%, 2013–2015), Malaysia (33.9%, 2008–2019), Indonesia (31.7%, 2015–2018) and Thailand (29.7%, 2011–2014), and also higher than rates in other Asian countries, including China (20.8%, 2011–2016), South Korea (32.9%, 2012–2013) and India (45.0%, 2014–2016). However, the rate in Vietnam was slightly lower than rates in Cambodia (49.6%, 2010–2016), Myanmar (50.0%, 2009–2014) and Laos (52.4%, 2009–2015) (Chung et al., 2015; Angkeabos et al., 2018; Bonifacio et al., 2018; SoukAloun et al., 2018; Theingi Win et al., 2018; Tian et al., 2018; Athiyyah et al., 2019; Gupta et al., 2019; Tacharoenmuang et al., 2020).

Although the overall RV positivity rate was high, it decreased between 2013 and 2018, and there was only one death due to RVGE during the entire study period. Recently, the global incidence of RV

Table 2
Risk analysis for rotavirus (RV) gastroenteritis.

Variables	Crude				Adjusted			
	OR	95% CI		*P*-value	OR	95% CI		*P*-value
All cases of gastroenteritis (n = 5163[a])								
Age in months								
<6	Reference	—	—	—	Reference	—	—	—
6–11	1.7	1.4	2.1	<0.001	1.7	1.4	2.1	<0.001
12–23	2.5	2.1	3.1	<0.001	2.6	2.1	3.2	<0.001
24–59	2.7	2.1	3.4	<0.001	2.6	2.0	3.4	<0.001
Sex								
Male	Reference	—	—	—	Reference	—	—	—
Female	1.0	0.9	1.1	0.93	1.0	0.9	1.1	0.98
Admission year								
2013	Reference	—	—	—	Reference	—	—	—
2014	0.7	0.6	0.8	<0.001	0.7	0.5	0.8	<0.001
2015	0.7	0.6	0.8	<0.001	0.7	0.5	0.8	<0.001
2016	0.7	0.6	0.8	<0.001	0.7	0.5	0.8	<0.001
2017	0.7	0.6	0.8	<0.001	0.6	0.5	0.7	<0.001
2018	0.6	0.5	0.8	<0.001	0.5	0.4	0.6	<0.001
Seasonality								
Rainy season (May–October)	Reference	—	—	—	Reference	—	—	—
Dry season (November–April)	2.4	2.1	2.7	<0.001	2.4	2.1	2.6	<0.001
Geographical distribution								
South-eastern	Reference	—	—	—	Reference	—	—	—
South-western	1.3	1.1	1.5	<0.001	1.3	1.1	1.5	<0.001
Other	1.2	1.02	1.5	0.03	1.3	1.1	1.5	0.01
RV vaccination								
Unvaccinated	Reference	—	—	—	Reference	—	—	—
Vaccinated								
Incomplete	0.4	0.2	0.7	0.001	0.4	0.3	0.8	0.004
Complete	0.2	0.1	0.3	<0.0001	0.2	0.1	0.3	<0.001
Severe gastroenteritis (Vesikari score $\geq$ 11) (n = 1277[b])								
Age in months								
<6	Reference	—	—	—	Reference	—	—	—
6–11	1.5	0.97	2.3	0.07	1.5	0.96	2.4	0.08
12–23	2.3	1.5	3.6	<0.001	2.3	1.5	3.7	<0.001
24–59	2.9	1.7	4.8	<0.001	2.7	1.6	4.6	<0.001
Sex								
Male	Reference	—	—	—	Reference	—	—	—
Female	0.9	0.8	1.2	0.64	0.9	0.7	1.1	0.37
Admission year								
2015	Reference	—	—	—	Reference	—	—	—
2016	1.3	0.95	1.8	0.09	1.2	0.9	1.7	0.21
2017	1.0	0.7	1.4	1.00	0.9	0.6	1.2	0.34
2018	0.9	0.7	1.2	0.51	0.8	0.6	1.05	0.10
Seasonality								
Rainy season (May–October)	Reference	—	—	—	Reference	—	—	—
Dry season (November–April)	2.0	1.6	2.5	<0.0001	2.0	1.6	2.5	<0.001
Geographical distribution								
South-eastern	Reference	—	—	—	Reference	—	—	—
South-western (Mekong River Delta)	1.2	0.9	1.5	0.19	1.2	0.95	1.6	0.11
Other	1.3	0.9	1.9	0.17	1.3	0.9	1.9	0.16
RV vaccination								
Unvaccinated	Reference	—	—	—	Reference	—	—	—
Vaccinated								
Incomplete	0.1	0.02	1.2	0.07	0.3	0.03	2.3	0.23
Complete	0.2	0.1	0.4	<0.0001	0.2	0.1	0.4	<0.001

OR, odds ratio; CI, confidence interval; ORS, oral rehydration solution; IV, intravenous; SD, standard deviation.
[a] Thirteen cases involving missing data were excluded from the analysis.
[b] Three cases involving missing data were excluded from the analysis.

infection and RV-related mortality have decreased (Debellut et al., 2019; Lestari et al., 2020). This has been attributed not only to an increase in RV vaccine coverage but also to an increase in living standards due to an increase in income in LMICs (Debellut et al., 2019). Lestari et al. (2020) reported that improvements in gross domestic product (GDP) were associated with a reduction in RV mortality in South-east Asian countries such as Myanmar, Laos and Thailand, regardless of RV vaccination coverage. In Vietnam, at the time of this study, RV vaccination was not included in the NIP, and RV vaccine coverage was low (3.9%). However, Vietnam experienced consistent economic growth (an average annual increase of 6.4% in GDP over the 6-year study period), which may have led to a decrease in RVGE rates. Likewise, the RVGE incidence rate was lower in the south-eastern region, which has higher socio-economic status including a higher GDP and lower child mortality rate than the south-western region. These results highlight the importance of improvement in socio-economic status along with improved health and sanitation to reduce the incidence of RV infection.

The major shift in genotype distribution from 2013 to 2018 is notable. Currently, six major genotypes (G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] and G12P[8]) account for approximately 90% of all human RV infections in many regions worldwide (Van Man et al., 2001; Trang et al., 2014; Debellut et al., 2019). Until recently, G1P

Table 3
Rotavirus genotypes in children with rotavirus (RV) gastroenteritis (n = 1105).

	Total		RV vaccine group		Non-RV vaccine group		
RV genotypes	*n*	(%)	*n*	(%)	*n*	(%)	*P*-value
Single							
All single genotypes	1086	100.0	16	100.0	1070	100.0	
G3P[8]	478	43.1	5	31.3	473	43.4	0.30
G8P[8]	218	19.7	3	18.8	215	19.7	0.89
G1P[8]	143	12.9	4	25	139	12.8	0.16
G2P[4]	140	12.7	4	25	136	12.4	0.14
G9P[8]	38	3.4	0	0	38	3.5	–
G2P[8]	20	1.8	0	0	20	1.8	–
Other[a]	49	4.1	0	0	49	4.5	–
Combined							
All combined genotypes	19	1.7	0	0	19	1.7	–
G1P[8]/G3P[8]	9	0.8	0	0	9	0.8	–
G1P[4]/G3P[4]	2	0.2	0	0	2	0.2	–
G2P[4]/G2P[8]	2	0.2	0	0	2	0.2	–
G1P[4]/G1P[8]	1	0.1	0	0	1	0.1	–
G3P[8]/G4P[8]	1	0.1	0	0	1	0.1	–
G1P[6]/G3P[8]	1	0.1	0	0	1	0.1	–
G8P[4]/G8P[10]	1	0.1	0	0	1	0.1	–
G8P[4]/G8P[8]	1	0.1	0	0	1	0.1	–
G9P[4]/G9P[8]	1	0.1	0	0	1	0.1	–
Total	1105	100.0	16	100.0	1089	100.0	

Nt, non-typeable.
[a] Includes 11 G1P[4], nine G3P[4], five G3P[9], three G1P[6], three G4P[6], three GNtP[8], two G3P[6], two G3P[Nt], two G4P[8], two G9P[6], one G3P[11], one G5P[19], one G8P[4], one G8P[6], one G9P[4], one G9P[Nt] and one undetermined case.

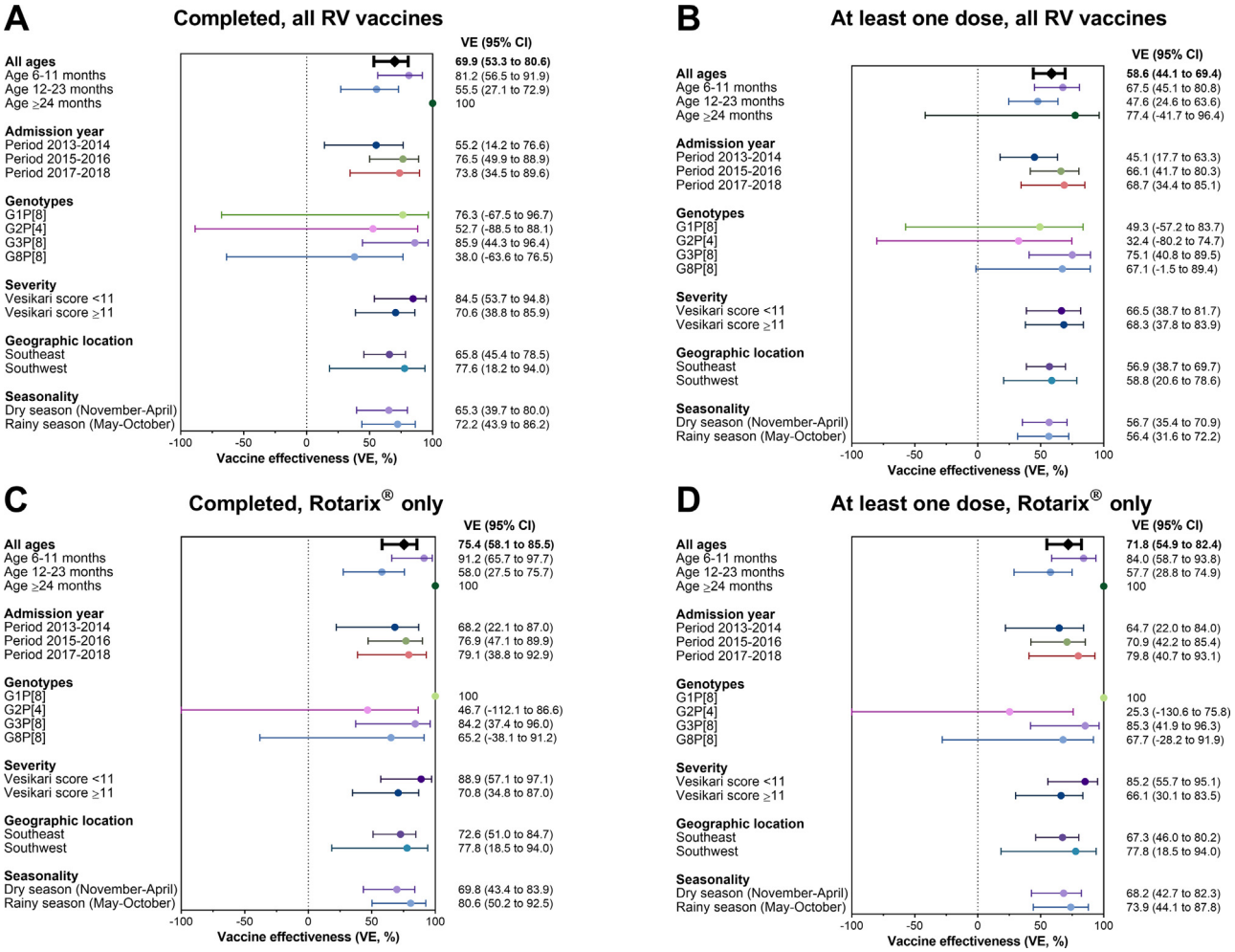


Figure 3. Vaccine effectiveness (VE) in hospitalized children with rotavirus (RV) gastroenteritis. The overall VE analysis included 4593 patients (>6 months of age) with RV-vaccine-related information; 3376 patients with available RV genotype data were included in the genotyping analysis, and 4085 patients with available geographic data were included in the geographic location analysis. (A) VE in patients who completed the vaccination course regardless of RV vaccine type. (B) VE in patients who received at least one dose of RV vaccine dose regardless of vaccine type. (C) VE in patients who completed the Rotarix vaccination course. (D) VE in patients who received at least one dose of Rotarix.

[8] was the most prevalent G/P genotype; however, G3P[8] has emerged as a predominant genotype in countries in Asia (Pakistan, Japan), South America (Argentina) and Europe (Germany, Spain) (Esposito et al., 2019). G3P[8] was the most prevalent genotype in the present study, followed by G8P[8], G1P[8] and G2P[4]. A similar genotype distribution was observed in studies conducted in neighbouring ASEAN countries between 2010 and 2019 (Lestari et al., 2020; Tacharoenmuang et al., 2020). In Thailand, where RV vaccination was not included in the NIP until 2019, the prevalence of G1P[8] (the most prevalent genotype) decreased while the prevalence of G3P[8] increased markedly between January 2014 and September 2016 (World Health Organization, 2013a). Moreover, the prevalence of infections caused by the G2P[4] genotype has increased in children and adults in several countries using the Rotarix vaccine (Tacharoenmuang et al., 2020). The increased prevalence of G3P[8] and G2P[4] can be attributed to the selective pressure of RV vaccines, which appear to have lower VE against these genotypes (Van Man et al., 2001; Gupta et al., 2019; Folorunso and Sebolai, 2020). However, despite the fact that RV vaccines had not been introduced into the NIP in Vietnam at the time of the study, the G2P[4] strain was the fourth most prevalent genotype, and its prevalence fluctuated throughout the study period. VE against G2P[4] has been reported to be lower than that for other major genotypes, as observed in this study. Therefore, ongoing surveillance of the dynamics of RV genotype, including the G2P[4] genotype, should continue after the introduction of RV vaccine in the NIP.

The overall VE assessed in children hospitalized with RVGE was 58.6–69.9% according to vaccination status. RV VE in other studies conducted in LMICs has ranged from 51% to 64%, which is lower than that reported in high-income countries (85–98%) (Tu et al., 2012; Pietsch and Liebert, 2019; Folorunso and Sebolai, 2020). To date, three major RV vaccine studies have been conducted in Vietnam. A phase 3 trial of RotaTeq reported VE of 63.9% (Zaman et al., 2010). A trial of Rotarix found seroconversion rates of 63.3–81.5% (Anh et al., 2011). A phase 2 trial of Rotavin-M1 found a seroconversion rate similar to that for Rotarix (Anh et al., 2012). VE by genotype was only reported in the RotaTeq vaccine study. The seroconversion rate of G2 (9.9%) was lower than the rates for G1 (32.1%), G3 (28.2%), G4 (18.3%) and P1A[8] (27.5%). The present study reported VE during a period when RV vaccination was only available in the private sector in Vietnam; the majority of those vaccinated received Rotarix. RV vaccines have been shown to be effective, even in settings where the vaccination rate is extremely low; however, VE varies by genotype. VE against G2P[4] appears to be lower than VE for other major genotypes. However, as there were only four cases of RVGE due to G2P[4] RV in the RV vaccine group, this result should be interpreted with caution.

This study has several limitations. First, it only included sentinel surveillance data from southern Vietnam, which may not be representative of the whole country. Second, as non-hospitalized children were not included in the study, the results do not represent the epidemiology and genotype distribution in children in the community. However, the population of southern Vietnam accounts for more than one-third of the total population of Vietnam, and this study was conducted on >5000 children hospitalized with acute gastroenteritis. Finally, this study had insufficient statistical power to evaluate VE for some genotypes because of the small number of children who had been vaccinated. In addition, it is possible that infants in families with high socio-economic status may have a higher vaccination rate.

In conclusion, RV infection still accounts for nearly half of cases of acute watery diarrhoea among hospitalized children aged <5 years in southern Vietnam. The RV genotype changed dynamically from year to year, and the estimated VE based on vaccination history was 58.6–69.9%. RV vaccines will soon be introduced into the NIP in Vietnam, and continuous surveillance of RV genotypes is essential to evaluate the effectiveness of the vaccination programme.

Authors' contributions

DTTT and JMK were responsible for all facets of this study and prepared the manuscript. TVN, JSY and NTHT contributed to the study design and analysis. TVH, TAH, TDN, QLC and QDP were involved in data collection and data management at the Pasteur Institute. HTN, NTHT and PLH contributed to data collection and data management at Children Hospital 1. JGA and SY contributed to data analysis. TTTN and TMTP performed the laboratory tests. All authors read and approved the final manuscript.

Conflict of interest

None declared.

Funding

This work was supported by the Basic Science Research Programme through the National Research Foundation of Korea, funded by the Ministry of Education (2019032869). The Rotavirus Sentinel Surveillance was supported by a grant from the WHO Vietnam Country Office to the Pasteur Institute, Ho Chi Minh City.

Acknowledgements

The authors wish to thank the patients for their participation in this study; and the National Institute of Hygiene and Epidemiology and the WHO Representative Office in Vietnam for their technical and financial support to the Rotavirus Sentinel Surveillance. The authors also wish to thank the Southern Vietnam Rotavirus Sentinel Surveillance Team for making the data available for this study, including: Tram Thi Quynh Phan, Phuong Kim Vo, Tuyen Thi Tran, Tram Thi Ngoc Nguyen, Khanh My Tran, Ut Thi Ngo, Ngoc Thi Bich Le, Hieu Ngoc Nguyen and Thuy Thi Minh Nguyen.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.02.047.

References

Ali Z, Harastani H, Hammadi M, Reslan L, Ghanem S, Hajar F, et al. Rotavirus genotypes and vaccine effectiveness from a sentinel, hospital-based, surveillance study for three consecutive rotavirus seasons in Lebanon. PLoS One 2016;11:e0161345.

Angkeabos N, Rin E, Vichit O, Chea C, Tech N, Payne DC, et al. Pediatric hospitalizations attributable to rotavirus gastroenteritis among Cambodian children: seven years of active surveillance, 2010–2016. Vaccine 2018;36:7856–61.

Anh DD, Thiem VD, Fischer TK, Canh DG, Minh TT, Tho LH, et al. The burden of rotavirus diarrhea in Khanh Hoa Province, Vietnam: baseline assessment for a rotavirus vaccine trial. Pediatr Infect Dis J 2006;25:37–40.

Anh DD, Carlos CC, Thiem DV, Hutagalung Y, Gatchalian S, Bock HL, 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;29:2029–36.

Anh DD, Van Trang N, Thiem VD, Anh NTH, Mao ND, Wang Y, et al. A dose-escalation safety and immunogenicity study of a new live attenuated human rotavirus vaccine (Rotavin-M1) in Vietnamese children. Vaccine 2012;30:A114–21.

Athiyyah AF, Utsumi T, Wahyuni RM, Dinana Z, Yamani LN, Soetjipto, et al. Molecular epidemiology and clinical features of rotavirus infection among pediatric patients in East Java, Indonesia during 2015–2018: dynamic changes in rotavirus genotypes from equine-Like G3 to typical human G1/G3. Front Microbiol 2019;10:940.

Bodhidatta L, Lan NT, Hien BT, Lai NV, Srijan A, Serichantalergs O, et al. Rotavirus disease in young children from Hanoi, Vietnam. Pediatr Infect Dis J 2007;26:325–8.
Bonifacio J, Lupisan S, Roque Jr. V, Ducusin MJ, Grabovac V, Batmunkh N, et al. Molecular characterization of rotavirus diarrhea among children aged under five years in the Philippines, 2013–2015. Vaccine 2018;36:7888–93.
Chung JY, Kim MS, Jung TW, Kim SJ, Kang JH, Han SB, et al. Detection of rotavirus genotypes in Korea 5 years after the introduction of rotavirus vaccines. J Korean Med Sci 2015;30:1471–5.
Debellut F, Clark A, Pecenka C, Tate J, Baral R, Sanderson C, et al. Re-evaluating the potential impact and cost-effectiveness of rotavirus vaccination in 73 Gavi countries: a modelling study. Lancet Glob Health 2019;7:e1664–74.
Esposito S, Camilloni B, Bianchini S, Ianiro G, Polinori I, Farinelli E, et al. First detection of a reassortant G3P[8] rotavirus A strain in Italy: a case report in an 8-year-old child. Virol J 2019;16:64.
Fischer TK, Anh DD, Antil L, Cat ND, Kilgore PE, Thiem VD, et al. Health care costs of diarrheal disease and estimates of the cost-effectiveness of rotavirus vaccination in Vietnam. J Infect Dis 2005;192:1720–6.
Folorunso OS, Sebolai OM. Overview of the development, impacts, and challenges of live-attenuated oral rotavirus vaccines. Vaccines 2020;8:, doi:http://dx.doi.org/10.3390/vaccines8030341.
GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117–71.
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;18:1211–28.
Gupta S, Chaudhary S, Bubber P, Ray P. Epidemiology and genetic diversity of group A rotavirus in acute diarrhea patients in pre-vaccination era in Himachal Pradesh. India. Vaccine 2019;37:5350–6.
Huyen DTT, Hong DT, Trung NT, Hoa TTN, Oanh NK, Thang HV, et al. Epidemiology of acute diarrhea caused by rotavirus in sentinel surveillance sites of Vietnam, 2012–2015. Vaccine 2018;36:7894–900.
Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries: a prospective, case–control study. Lancet 2013;382:209–22.
Lestari FB, Vongpunsawad S, Wanlapakorn N, Poovorawan Y. Rotavirus infection in children in Southeast Asia 2008–2018: disease burden, genotype distribution, seasonality, and vaccination. J Biomed Sci 2020;27:66.
Nguyen TV, Le Van P, Le Huy C, Weintraub A. Diarrhea caused by rotavirus in children less than 5 years of age in Hanoi, Vietnam. J Clin Microbiol 2004;42:5745–50.
Pietsch C, Liebert UG. Rotavirus vaccine effectiveness in preventing hospitalizations due to gastroenteritis: a descriptive epidemiological study from Germany. Clin Microbiol Infect 2019;25:102–6.
Roczo-Farkas S, Kirkwood CD, Cowley D, Barnes GL, Bishop RF, Bogdanovic-Sakran N, et al. The impact of rotavirus vaccines on genotype diversity: a comprehensive analysis of 2 decades of Australian surveillance data. J Infect Dis 2018;218:546–54.
Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354:11–22.
SoukAloun D, Douangbouphaa V, Phetsouvanh R, Sibounheuang B, Vongsouvat M, Chanmala K, et al. Rotavirus diarrhea in hospitalized children under 5 years of age in Vientiane, Lao PDR, 2009–2015. Vaccine 2018;36:7878–82.
Tacharoenmuang R, Komoto S, Guntapong R, Upachai S, Singchai P, Ide T, et al. High prevalence of equine-like G3P[8] rotavirus in children and adults with acute gastroenteritis in Thailand. J Med Virol 2020;92:174–86.
Tate JE, Burton AH, Boschi-Pinto C, Parashar UD, Agocs M, Serhan F, et al. Global, regional, and national estimates of rotavirus mortality in children <5 years of age, 2000–2013. Clin Infect Dis 2016;62(Suppl. 2):S96–105.
Theingi Win M, Hlaing Myat T, Ye Myint K, Khin Mar A, Mo Mo W, Htin L, et al. Sentinel surveillance for rotavirus in children <5 years of age admitted for diarrheal illness to Yangon Children's Hospital, Myanmar, 2009–2014. Vaccine 2018;36:7832–5.
Tian Y, Chughtai AA, Gao Z, Yan H, Chen Y, Liu B, et al. Prevalence and genotypes of group A rotavirus among outpatient children under five years old with diarrhea in Beijing, China, 2011–2016. BMC Infect Dis 2018;18:497.
Trang NV, Braeckman T, Lernout T, Hau VTB, Anh LTK, Luan LT, et al. Prevalence of rotavirus antibodies in breast milk and inhibitory effects to rotavirus vaccines. Hum Vaccin Immunother 2014;10:3681–7.
Tu HA, Rozenbaum MH, Coyte PC, Li SC, Woerdenbag HJ, Postma MJ. Health economics of rotavirus immunization in Vietnam: potentials for favorable cost-effectiveness in developing countries. Vaccine 2012;30:1521–8.
Van Man N, Van Trang N, Lien HP, Trach DD, Thanh NTH, Van Tu P, et al. The epidemiology and disease burden of rotavirus in vietnam: sentinel surveillance at 6 hospitals. J Infect Dis 2001;183:1707–12.
World Health Organization. Introduction of rotavirus vaccines: information for policy makers, programme managers, and health workers. Geneva: WHO; 2013.
World Health Organization. Rotavirus vaccine position paper. Wkly Epidemiol Rec 2013b;88:49–64.
World Health Organization. Immunization coverage. Geneva: WHO; 2020.
Zaman K, Dang DA, Victor JC, Shin S, Yunus M, Dallas MJ, 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;376:615–23.