

Clinical and molecular epidemic characterization of rotavirus infection among children under five years old in Shandong province, China.

Shixiao Dong

Shandong University Qilu Hospital

Deyu Huang

The Affiliated Hospital of Qingdao University

Zheng Wang

Shandong University Qilu Hospital

Guanyou Zhang

Shandong University Qilu Hospital

Fengjuan Zhang

The Affiliated Hospital of Qingdao University

Lintao Sai (✉ sailintao@sdu.edu.cn)

Shandong University Qilu Hospital <https://orcid.org/0000-0003-0377-6667>

Research Article

Keywords: rotavirus, clinical and molecular epidemic characterization, children

Posted Date: April 16th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-419348/v1>

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Abstract

Rotavirus was the an important causative agent of acute gastroenteritis in children. In China, rotavirus was positive in approximately 30% of the diarrhea children and become a serious public problem. This study was carried out to investigate the clinical and molecular epidemic characterization of rotavirus infection among children under 5 years old with acute diarrhea in Shandong province, China. From July 2017 to June 2018, a total of 1211 fecal specimens were detected and the prevalence of rotavirus infection was 32.12%. The mean age of positive children was 12.2 ± 10.9 months and the highest infection rate was observed in children aged 7–12 months with a rate of 41.64%. G9P[8] (76.61%) was the most prevalent combinations followed by G2P[4] (7.20%), G3P[8] (3.60%) and G9P[4] (2.06%). In addition to diarrhea, vomiting, fever and dehydration were the most common accompanied symptoms. In general, there was no significant difference in clinical manifestations among different age groups. However, the clinical manifestations between vaccinated and unvaccinated children were significantly different. Vaccinated children showed lower incidence and frequency of vomiting, lower incidence and degree of dehydration, lower incidence of severe cases than unvaccinated children. The findings suggested necessary to continue rotavirus strains surveillance in order to monitor the change of prevalent genotype. Moreover, introducing vaccine into national immunization program to prevent and control rotavirus infections is needed in China.

Introduction

Rotavirus is the most common causative agent of acute gastroenteritis in children under 5 years old and rotavirus gastroenteritis is the leading cause of severe and fatal diarrhea in this age group. Globally, rotavirus infection causes an estimated about 10 million severe cases leading to 118,000-183,000 deaths every year, in which approximately 41% of deaths occur in Asia [1, 2].

Rotavirus as a member of the family *Reoviridae* is a non-enveloped and double-stranded RNA virus. The genome surrounded by a triple-layered capsid consists of 11 segments, which encode six structural proteins (VP1-4 and VP6-7) and six nonstructural proteins (NSP1-6). Rotaviruses are classified into 7 antigenic groups (A-G) according to the various serotypes of VP6 protein, in which group A rotaviruses (RVA) are the most important causative agents associated with acute diarrhea in children [3]. The two outer capsid proteins, VP7 and VP4, are specific epitope and can induce specific protective immune responses, based on which rotavirus vaccines are developed. The glycoprotein VP7 defines G genotype, while the protease-sensitive protein VP4 determines P genotype. G1-G4, G9 and G12 are the most prevalent G genotype, whilst P[4] and P[8] are the most common P genotype worldwide. G and P genotype can be combined, therefore dual nomenclature system is used to determine rotavirus strains. The most prevalent G-P combinations are G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] [4, 5].

Rotavirus gastroenteritis in young children is a serious public health problem in both developed and developing countries. In view of the lack of effective drug, vaccination is an effective strategy for the prevention and control of rotavirus infections. By the end of October 2019, 102 countries had

implemented rotavirus vaccines in their national immunization program, which showed remarkable decline of severe cases and deaths [6]. In China, two vaccines, a monovalent vaccine LLR (Lanzhou lamb rotavirus vaccine) and a pentavalent vaccine RotaTeq (RV5, Merck Vaccine, NJ, USA), had been approved and licensed since 2000 and 2018, respectively. Unfortunately, none of them was introduced in the national immunization program. Children could choose to be vaccinated voluntarily, but the willingness was not strong. Therefore, the rotavirus infection was still very severe in China. WHO estimated that 9072 children under 5 years old died from diarrhea in China in 2013, of which 3191 (35.2%) children died from rotavirus gastroenteritis [1]. A seven-year continuous surveillance from 2009 to 2015 in China demonstrated that 30% of diarrhea cases among children under 5 years old were positive for rotavirus [7]. Moreover, the cost of treatment for rotavirus gastroenteritis in China was higher than any other countries in Asia [8].

The epidemiological feature of rotavirus infection is an important basis to develop vaccine and determine to introduce vaccine in the national immunization program. The present study aimed to investigate the prevalent genotypes of rotavirus and clinical manifestations, reveal the epidemiological features of rotavirus infection, evaluate the disease burden and further improve the prevention and control of rotavirus gastroenteritis.

Materials And Methods

Children under 5 years old with acute gastroenteritis were enrolled from two large general hospitals (Qilu Hospital of Shandong University and Affiliated Hospital of Qingdao University) in Shandong province between July 2017 and June 2018. Acute gastroenteritis was characterized by the sudden onset of diarrhea (more than 3 looser or watery stools) with or without vomiting within a 24-h period. Children with the presence of pus and blood in the stool were excluded from this surveillance. Informed consent was obtained from all children's parents. This study was approved by ethics committee on scientific research of Shandong University Qilu Hospital.

Specimens collection and management

Fecal specimens were freshly collected from every children and divided into two parts. One part was tested for rotavirus antigen at once using a Fecal Rotavirus Antigen ELISA Kit (EDI, CA, USA). The other part was made into a 10% (m/v) suspension with PBS (pH 7.2) and the suspension was centrifuged at 10000×g for 5 minutes. Then, the supernatants were collected and stored at -70°C for the following test.

Demographic and clinical data collection

Demographic information included gender, age and vaccination history, while the clinical data consisted of duration and number of diarrhea and vomiting, degree of fever, severity of dehydration and treatment. The severity of infection was assessed using a scoring system adapted from the Vesikari clinical severity scoring system (< 7 for mild, 7–10 for moderate, ≥ 11 for severe).

VP7 and VP4 detection

The samples positive for rotavirus antigen were further tested to detect the genotypes of VP7 and VP4 using reverse-transcription polymerase chain reaction (RT-PCR). Viral RNA was extracted from 200µl of the supernatant using a Virus RNA Isolation Kit (Sangon, Shanghai, China) according to the manufacture's instructions. Complementary DNA was synthesized by RT using random primers and used as template. VP7 and VP4 genes were typed in PCR using published oligonucleotide primers, which could amplify G-genotypes (G1, G2, G3, G4, G8, G9, G10 and G12) and P-genotypes (P[4], P[6], P[8], P[9], P[10] and P[11]) [9, 10]. All amplified products were visualised in a 2.0% agarose gel using a ultraviolet transilluminator and the genotypes were determined based on the size of the amplicon.

Statistical analysis

Data from this study was analyzed using SPSS (version 25.0) with Chi-square test, t-test and Kruskal-Wallis test. Statistical significance was defined as a P value less than 0.05.

Results

Between July 2017 and June 2018, a total of 1211 stool specimens were collected from children under 5 years old with acute gastroenteritis. The mean age of enrolled children was 13.4 ± 12.2 months and the ratio of male to female was 1.41. Overall, the detection rates of RVA was 32.12% (389/1211). The mean age of positive children was 12.2 ± 10.9 months and the ratio of male to female was 1.49. The RVA infection rates of male and female were 32.86% (233/709) and 31.08% (156/502), respectively. The difference of infection rates between boys and girls was no statistically significant ($P > 0.05$).

The enrolled children were divided into four age groups: 0–6 months, 7–12 months, 13–24 months and 25–60 months. RVA infections were observed in all age groups in this study. The distribution of age and infection rate were shown in Table 1. For each group, the group with the highest infection rate was 7–12 months group (37.07%, 162/437), followed by 0–6 months group (31.71%, 124/391), 13–24 months group (28.77%, 61/212) and 25–60 months group (24.56%, 42/171). The difference of infection rate among the four age groups was statistically significant ($P < 0.05$). Among RVA infected children, the highest infection rate was observed in children aged 7–12 months (41.64%, 162/389), followed by children aged 0–6 months (31.88%, 124/389), children aged 13–24 months (15.68%, 61/389) and children aged 25–60 months (10.80%, 42/389).

389 rotavirus positive samples were further identified by RT-PCR for G-genotype and P-genotype and the distribution of detected genotypes were shown in Fig. 1. 375 (96.40%, 375/389) samples were successfully typed as G-genotype, in which six mixed G-genotypes were detected. The remaining fourteen samples (3.60%, 14/389) could not be typed. G9 (80.46%, 313/389) was the most common G-genotype followed by G2 (7.97%, 31/389), G3 (4.63%, 18/389), G1 (1.29%, 5/389) and G4 (0.51%, 2/389). 369 (94.86%, 369/389) samples were identified as P-genotype, in which two mixed P-genotype were observed. Meanwhile, twenty (5.14%, 20/389) samples were P nontypeable. The most prevalent P-genotype was P[8] (82.78%, 322/389) followed by P[4] (9.77%, 38/389) and P[6] (1.80%, 7/389). For G and P combinations, G9P[8] (76.61%, 298/389) was the most prevalent combinations followed by G2P[4]

(7.20%, 28/389), G3P[8] (3.60%, 14/389) and G9P[4] (2.06%, 8/389). A number of rare G and P combinations were detected including G1P[8], G9P[6], G2P[8], G4P[8], G3P[4] and G3P[6]. The distribution of G and P combinations in every month was shown in Fig. 2.

Table 1. Distribution of age and infection rate of the four age groups.

	Age group				Total	P
	0-6 months	7-12 months	13-24 months	25-60 months		
Enrolled children	391 (32.29%)	437 (36.08%)	212 (17.51%)	171 (14.12%)	1211	-
Infected children	124 (31.88%)	162 (41.64%)	61 (15.68%)	42 (10.80%)	389	-
Infection rate	31.71%	37.07%	28.77%	24.56%	32.12%	0.533

In our study, rotavirus infections had obvious seasonal distribution, which occurred throughout the year and peaked from October to the next March (Fig. 3).

The main clinical manifestations of RVA infection shown in Table 2 included diarrhea, vomiting, fever and dehydration. Among 389 RVA positive children, the mean frequency of diarrhea was 5.49 ± 1.13 episodes/day, and 97.43% (379/389) of infected children experienced diarrhea more than 3 episodes/day. The incidence of vomiting was 83.55% (325/389) and the mean frequency was 2.96 ± 0.88 episodes/day. 95.38% (310/325) of children vomited between two and four episodes/day. 263 (67.61%) infected children had fever and the mean body temperature was $38.21 \pm 0.64^{\circ}\text{C}$. More than half (57.41%) of the feverish children had temperature below 38.5°C . The incidence of dehydration was lower than that of vomiting and fever. The rate was 44.99% (175/389) and the mean degree of dehydration was $(3.61 \pm 1.50)\%$. The mean score obtained on the basis of adapted Vesikari clinical severity scoring system was 9.61 ± 3.18 . The clinical manifestations of 175 (44.99%) children were graded to severity, while 153 (39.33%) and 61 (15.68%) children were graded to moderate and mild, respectively.

No statistical significance was observed in the mean frequency of diarrhea among the four age groups ($P = 0.272$), while the mean frequency of vomiting was found to be statistically significant ($P = 0.006$). The rates of vomiting, fever and dehydration were not statistically significant among the four age groups. Similarly, the degree of fever and dehydration was not statistically significant. The average score was also not found to be statistically significant.

Among the 389 RVA infected children, 88 (22.62%) children had been vaccinated against rotavirus, while 301 (77.38%) children had not been vaccinated (shown in Table 3). Statistically significant incidences of severe manifestations was found between vaccinated and unvaccinated children (28.41% vs. 49.83%, $P <$

0.001). No statistical significance in frequency of diarrhea between them. The frequency and rate of vomiting were statistically significant between vaccinated and unvaccinated children ($P < 0.001$ and $P = 0.033$, respectively). The degree and rate of dehydration were also significantly different ($P < 0.001$ and $P = 0.036$, respectively). However, degree and rate of fever between them were not statistically significant ($P = 0.663$ and $P = 0.093$).

Table 2. Clinical manifestation of rotavirus infected children.

	0-6 M N=124	7-12 M N=162	13-24 M N=61	25-60 M N=42	P value	Total N=389
Diarrhea (episodes/day)	5.44 ±1.25	5.54 ±0.95	5.33 ±1.11	5.69 ±1.35	0.272	5.49 ±1.13
≤ 3	5 (4.03%)	0 (0.00%)	1 (1.64%)	4 (9.52%)	-	10 (2.57%)
4-5	62 (50.00%)	84 (51.85%)	35 (57.38%)	13 (30.95%)	-	194 (49.87%)
≥ 6	57 (45.97%)	78 (48.15%)	25 (40.98%)	25 (59.53%)	-	185 (47.56%)
Vomiting rate	98 (79.03%)	142 (87.65%)	51 (83.61%)	34 (80.95%)	0.258	325 (83.55%)
episodes/day	2.14±0.79	2.12±0.87	2.94±0.70	3.35±0.88	0.006	2.96±0.88
1	23 (23.47%)	34 (23.94%)	0 (0.00%)	15 (44.12%)	-	5 (1.54%)
2-4	75 (76.53%)	106 (74.65%)	51 (100%)	19(55.88%)	-	310 (95.38%)
≥ 5	0 (0.00%)	2 (1.41%)	0 (0.00%)	0 (0.00%)	-	10 (3.08%)
Fever rate	83 (66.94%)	109 (67.28%)	42 (68.85%)	29 (69.05%)	0.990	263 (67.61%)
Average T (°C)	38.24±0.70	38.24±0.65	38.21±0.64	38.28±0.58	0.986	38.21±0.64
37.1-38.4	47 (56.63%)	62 (56.88%)	24 (57.14%)	18 (62.07%)	-	151 (57.41%)
38.5-38.9	26 (31.32%)	33 (30.28%)	13 (30.95%)	7 (24.14%)	-	79 (30.04%)
≥ 39.0	10 (12.05%)	14 (12.84%)	5 (11.91%)	4 (13.79%)	-	33 (12.55%)
Dehydration rate	56 (45.16%)	74 (45.68%)	25 (40.98%)	20 (47.62%)	0.909	175 (44.99%)
Degree (%)	3.52±1.32	3.70±1.44	3.92±1.82	3.20±1.74	0.386	3.61±1.50
No	68 (54.84%)	88 (54.32%)	36 (59.02%)	22 (52.38%)	-	214 (55.01%)
1-5%	52 (41.93%)	61 (37.65%)	19 (31.15%)	17 (40.48%)	-	149 (38.30%)
≥ 6%	4 (3.23%)	13 (8.03%)	6 (9.83%)	3 (7.14%)	-	26 (6.69%)
Average Score	9.50±3.40	9.90±2.94	9.30±3.21	9.26±3.32	0.563	9.61±3.18

< 7	24 (19.35%)	17 (10.49%)	9 (14.75%)	11 (26.19%)	-	61 (15.68%)
7-10	40 (32.26%)	72 (44.45%)	28 (45.90%)	13 (30.95%)	-	153 (39.33%)
≥ 11	60 (48.39%)	73 (45.06%)	24 (39.35%)	18 (42.86%)	-	175 (44.99%)

Table 3. Clinical manifestation of vaccinated and unvaccinated children with rotavirous infection.

	Vaccinated patients (n=88)	Unvaccinated patients (n=301)	P value
Diarrhea (episodes/day)	5.32 ± 1.31	5.54 ± 1.12	0.335
Vomiting rate (%)	76.14% (67/88)	85.71% (258/301)	0.033
Vomiting (episodes/day)	2.86 ± 0.78	2.12 ± 0.84	<0.001
Fever rate (%)	60.23% (53/88)	69.77% (210/301)	0.093
Temperature (°C)	38.27 ± 0.68	38.23 ± 0.65	0.663
Dehydration rate (%)	35.23% (31/88)	47.84% (144/301)	0.036
Dehydration degree (%)	3.39 ± 1.15	3.67 ± 1.56	<0.001
Severity rate (%)	28.41% (25/88)	49.83% (150/301)	<0.001

Discussion

Rotavirus was one of the most important causative pathogen of acute gastroenteritis in children. In China, previous study had reported that rotavirus was positive in approximately 30% of the diarrhea children [11]. In this study, the rotavirus positive rate was 32.12%, which was consistent with the overall rate at country level. Nearly similar positive rates were also detected in some cities and province in China: Kunming (29.70%), Chongqing (30.46%), Jinan (34.30%) and Fujian (23.50%) [12–15]. In the face of the high rotavirus infection rate, increasing the coverage of vaccine is a more important strategy, in addition to encouraging early exclusive breastfeeding and improving environmental and dietary hygiene.

Although rotavirus infections could be seen in all age groups, infected children under 2 years old accounted for the vast majority. There was significant statistical difference in infection rates of the four age groups and the highest infection rate was seen in children aged 7–12 months. The mean age of rotavirus positive children was 12.2 ± 10.9 months, which were similar to some previous studies reported by Yongbo Kang, Yuanjun Zeng and Bingshan Wu [12, 13, 15]. These findings showed that rotavirus infections usually occurred in early childhood. Therefore, WHO suggested that children aged over six weeks should be vaccinated as soon as possible to protect against rotavirus infection [16].

Rotavirus infections occurred throughout the year and the peak of infections was observed from October to the next March. During the peak period, low temperature resulted in the decrease of outdoor activities and increase of indoor aggregation. In addition, the weakened UV intensity prolonged the survival time of the virus. These factors might lead to increased risk of infection.

Compared with P genotype, the substitution of G genotype was more common. The changing trend of G genotype in China was consistent with the global trend. G1 genotype was the main prevalent strain before 2001[17]. G3 genotype was the predominant strain from 2001 to 2010, while the proportion of G9 genotype had increased year by year [18]. Since 2010, G9 genotype had become the most common strain. The fluctuation of P genotype was relatively small and P[8] was the main epidemic strain. Because of the alteration of G genotype, the epidemic G and P combination changed correspondingly. The predominant combination had shifted from G1P[8] and G3P[8] to G9P[8], with significant increase of G9P[8] from 3.4% in 2009 to 60.9% in China [19]. In this study, G9 and P[8] were the predominant G and P genotype, respectively. Therefore, G9P[8] was the most common combination with a rate of 76.61%, which was similar to some previous reports from other provinces and cities in China [12, 13, 15, 20, 21].

Typical symptoms for rotavirus infections including diarrhea, vomiting, fever and dehydration. In addition to diarrhea, vomiting was the most common accompanied symptom followed by fever and dehydration. Among the four age groups, children aged 25–60 months showed the most obvious vomiting symptom while children aged 7–12 months showed the least vomiting. The rates of vomiting, fever and dehydration was no significant difference among the four groups. The frequency of diarrhea and the degree of fever and dehydration among each age group were also no significant difference. These findings indicated that the symptoms caused by rotavirus infection in different age groups were similar.

The mortality rate of children under 5 years old caused by rotavirus infection decreased by 43.6% all over the world from 2005 to 2015. 328,000 deaths of children under 5 years old had been reduced worldwide because of vaccination in 2016 [22]. Among 389 rotavirus infected children, 88 children had been vaccinated against rotavirus. Vaccinated children showed lower incidence and frequency of vomiting, lower incidence and degree of dehydration, lower incidence of severe cases than unvaccinated children. The comparison indicated that vaccination could effectively alleviate the symptoms.

In conclusion, a systematic investigation of rotavirus infections was carried out among children under 5 years old with acute gastroenteritis in Shandong province, China. Findings from this study showed that rotavirus was an important pathogen in children with acute gastroenteritis. Infections mainly occurred in early childhood and peaked in cooler season. G9P[8] was the most common combination during the study period. The typical symptoms included diarrhea, vomiting, fever and dehydration, which could be alleviated by vaccination. Ongoing surveillance of rotavirus epidemiology and introducing vaccine into national immunization program to prevent and control rotavirus infections is needed in China.

Declarations

Authors contribution

Lintao Sai and Shixiao Dong conceived and designed the experiments. Zheng Wang, Fengjuan Zhang and Guanyou Zhang performed the experiments. Lintao Sai, Shixiao Dong, Deyu Huang analyzed the data. Lintao Sai, Shixiao Dong drafted or revised the manuscript. All authors have approved the final article.

Acknowledgments

This study was partially funded by the Shandong Provincial Key Research and Development Program (2018 GSF118071). The authors thank the researchers from the department of clinical laboratory of the two hospitals for fecal specimens collection and detection.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Figures

Fig. 1

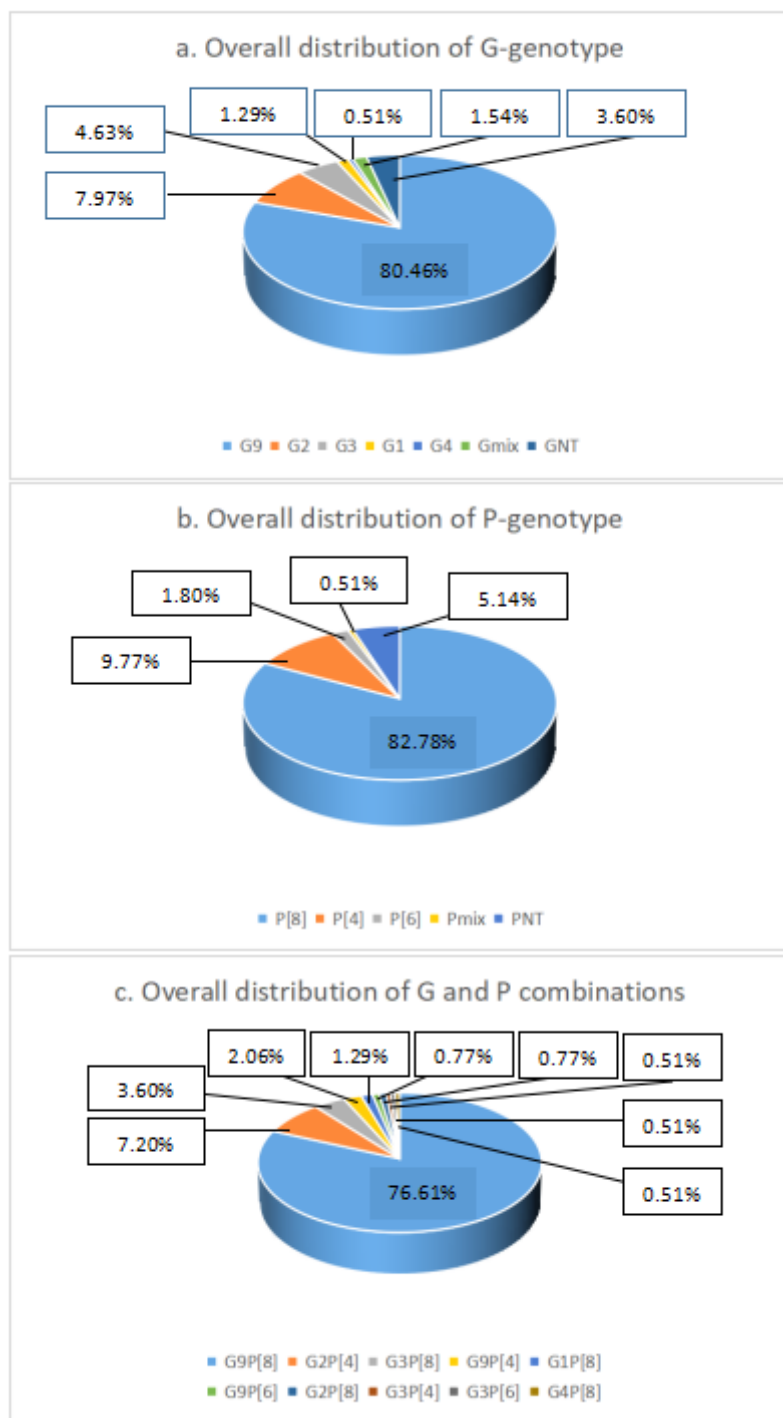


Figure 1

Distribution of detected rotavirus genotypes from this study. a Overall distribution of G-genotype. b Overall distribution of P-genotype. c Overall distribution of G and P combinations

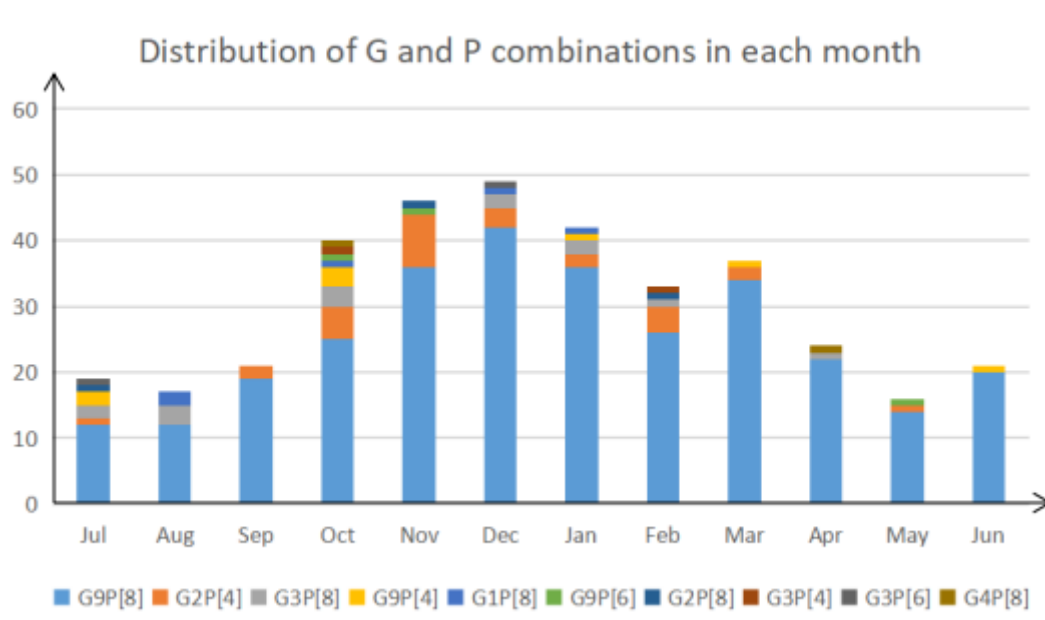


Figure 2

Distribution of G and P combinations in every month.

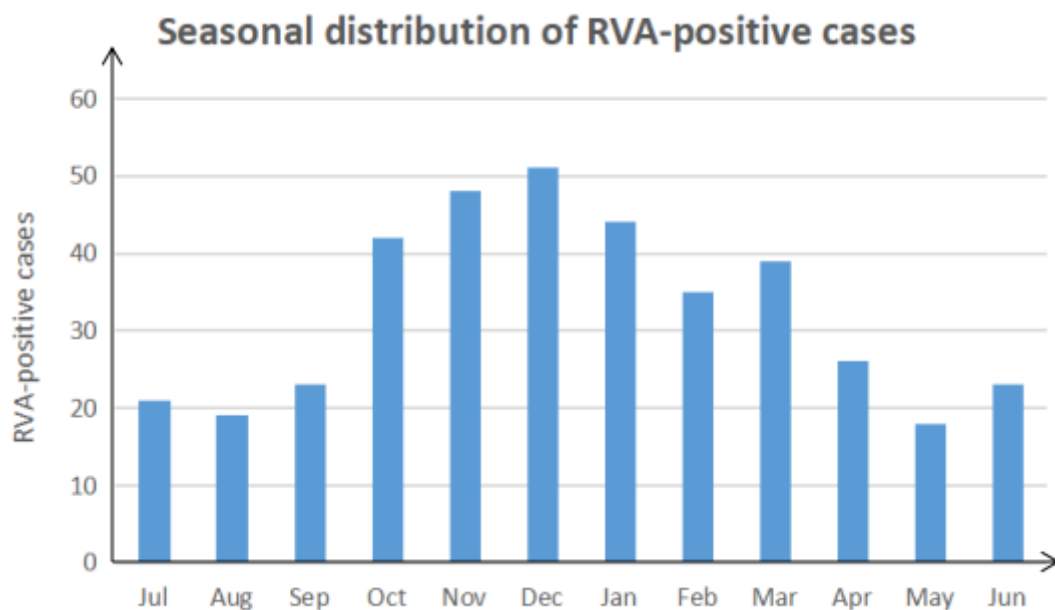


Figure 3

Monthly distribution of Rotavirus infections between July 2017 and June 2018. Infections occurred throughout the year and peaked from October to the next March. Rates of every month: 5.40%; 4.88%; 5.91%; 10.80%; 12.34%; 13.11%; 11.31%; 9.00%; 10.03%; 6.68%; 4.63%; 5.91%