Received: 14 July 2021 | Accepted: 25 November 2021

DOI: 10.1002/jmv.27484

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Genetic diversity of rotavirus strains circulating in Norway before and after the introduction of rotavirus vaccination in children

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Abstract

Globally, rotavirus (RV) is the leading cause of acute gastroenteritis (AGE) in young children under 5 years of age. Implementation of RV vaccination is expected to result in fewer cases of RV in the target population, but it is unknown if this also results in vaccine-induced virus strain replacement. Rotarix, a monovalent vaccine based on G1P[8] RV, was introduced in Norway in the children's immunization program in September 2014. The main aim of this study was to describe the diversity of RV circulating pre and post introduction of the RV vaccine in Norway and investigate changes in genotype distribution during the first 4 years after implementation. A total of 1108 samples were collected from children under 5 years enrolled with AGE from five large hospitals in Norway and were analyzed for RV by enzyme immunoassay (EIA). All positive results were genotyped by multiplex semi-nested reverse transcription PCR for identification of G and P types. In total, 487 of the 1108 (44%) samples, collected from the enrolled children, were positive for RV by EIA method which were further genotyped. G1P[8] was found to be the most common type of RV pre and post RV vaccine implementation followed by G9P[8]. There were neither geographical nor temporal differences in genotype dominance. Also, no apparent changes were shown in the genotype distribution in the post-vaccine era for years from 2015 to 2018. In 21.4% of the cases, vaccine strains were detected. Continuous RV genotype surveillance is vital for assessing the effectiveness of a vaccine program and monitoring for any emergence of vaccine-escape strains. Genotyping is also necessary to detect vaccine strains to avoid reporting false-positive cases of active RV infection in newly vaccinated cases.

KEYWORDS

AGE, genotyping, multiplex RT-PCR, rotarix, rotavirus

1 | INTRODUCTION

Rotavirus group A (RVA) is the leading cause of acute gastroenteritis (AGE) in young children under 5 years of age worldwide.[1,2] The burden of rotavirus in Norway was studied in hospital-based surveillance in 2007–8[3,4] and more recently in 2016 where rotavirus was reported to be the major cause of AGE in hospitalized children.[5] RVA belongs to the *Reoviridae* family and its genome consists of 11 double-stranded RNA segments which encode for six structural and six nonstructural viral proteins.[6] RVA can be divided into genotypes based on the G-protein (glycoprotein) and P-protein (protease-sensitive) with more than 200 possible combinations.

Global surveillance has identified a large number of rotavirus types in humans and frequently new types emerge due to the segmented genome and high reassortment rate of rotavirus. Geographical and temporal variations have been reported across continents, making it necessary to conduct regional genotype surveillance. The most dominant RV genotypes were G1P[8], G4P[8], G2P[4], G9P[8], G3P[8], G12P[8], and G9P[4] which represented 95% of all circulating genotypes.[7,8]

Severe rotavirus AGE disease can be prevented by vaccination. Implementation of rotavirus vaccination is expected to result in fewer cases of rotavirus in the target population, but it is unknown if this results in vaccine-induced virus strain replacement. Rotarix, a monovalent vaccine based on G1P[8] rotavirus, was introduced in Norway in the children's immunization program in September 2014. Simultaneously to detect vaccine failure and monitor effect, a nationwide laboratory surveillance was started and subsequently, rotavirus infection became a notifiable disease.

The main aim of this study was to describe the diversity of rotavirus circulating just before the introduction of the rotavirus vaccine in Norway and investigate changes in genotype distribution during the first 4 years after implementation. In addition, the sensitivity of rectal swabs versus bulk stool for genotyping of rotavirus strains was compared.

2 | MATERIALS AND METHODS

2.1 | Study population

The participants in this study were recruited from five large hospitals: Stavanger University Hospital in the Western Norway Regional Health Authority, St. Olavs University Hospital in the Central Region, and the following three in the South-Eastern region; Oslo University Hospital, Østfold Hospital, and Akershus University Hospital. The recruitment sites were chosen to obtain a geographical representation of nearly the whole country and to cover about 40% of the target population which are all children below 5 years of age hospitalized with AGE.

Primary inclusion criteria for the participants were AGE defined as ≥3 diarrhea episodes and/or one vomiting episode per 24 h. Eligibility criteria included age at the date of illness <5 years. Hospitalization was defined as being admitted to a hospital for more than 5 h. Only participants with at least 1 biological specimen were included in this study.

The study population included 1108 children consecutively enrolled during the period from January 27th, 2014 to May 31st, 2018. The mean age of the children was 17.6 months. The birth cohort before RV vaccine implementation was all children born in or before September 30th, 2014.

2.2 | Specimen collection

Paired samples from each participant, including bulk stool in a sterile container and Copan Fecal rectal swab containing Cary-Blair Transport Medium, were collected during the initial 48 h after hospital admission. The samples were immediately frozen at −70°C.

2.3 | Specimen preparation and viral nucleic acid extraction

A 10% fecal suspension with dilution buffer was prepared for each specimen from which 200 µl was utilized for nucleic acid extraction using the Viral NA Small Volume kit on the MagNA Pure 96 instrument according to manufacturer's instructions (Roche Applied Science).

2.4 | Rotavirus detection methods

All specimens from AGE cases were analyzed by a commercial enzyme-linked immunosorbent assay for the detection of rotavirus antigen by the RIDASCREEN kit (R-Biopharm AG) according to the manufacturer's protocol, and the test was carried out in an automated enzyme immunoassay (EIA) system, DS2® (Dynex Technologies Inc.).

2.5 | Molecular characterization and confirmation of rotavirus positive samples

All the positive samples for RV antigen were further analyzed by reverse transcription PCR (RT-PCR) after RNA was extracted. Genotyping was performed in a two-step procedure for identification of the G and P types by a multiplex PCR method as previously described.[7,8] Further, all G1P[8] samples were analyzed by an in-house RT-PCR for detection of Rotarix vaccine strains.[9,10]

3 | RESULTS

Out of the participating children with AGE, 487 tested positive for rotavirus by EIA, including 308 bulk stool samples and 179 rectal swabs that could be further characterized by genotyping (Figure 1). In birth cohorts born in 2014, 39.6% (439/1108) of the samples were positive for RV by EIA method, but in the following years, there was a

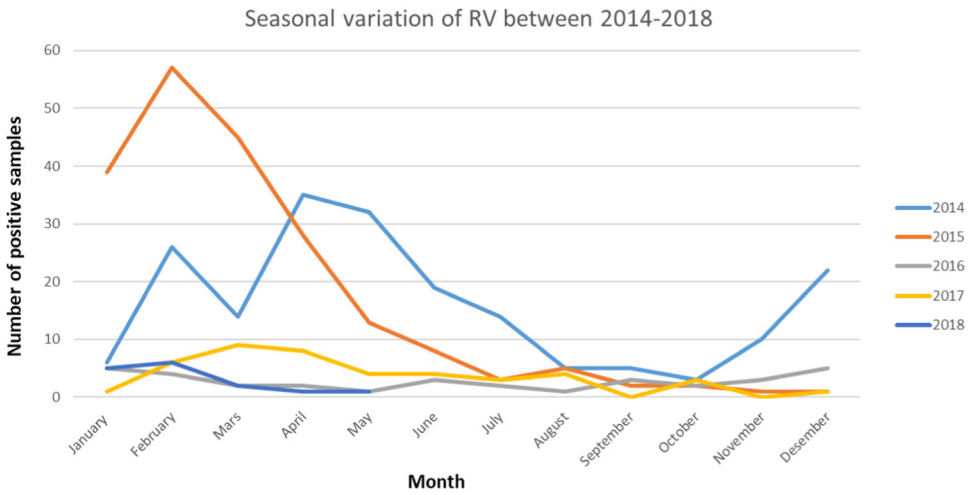

FIGURE 1 Rotavirus EIA positive results ($n = 487$) according to months per year. The graph shows the number of RV-positive cases after the vaccine was implemented in 2014 and the decrease in the following years. RV, rotavirus

TABLE 1 Rotavirus (RV) EIA samples tested in AGE cases per year

	2014	2015	2016	2017	2018	Total
Number of AGE cases tested by rotavirus antigen EIA test	327	373	213	153	42	1108
Total number of positive cases	192	204	33	43	15	487
Number of EIA positive that received 1 rotavirus vaccine dose (%)	0	1 (100)	0	0	0	1
Number of EIA positive that received 2 rotavirus vaccine doses (%)	0	0	8 (25)	17 (53)	7 (22)	32

Note: Number of RV antigen EIA method tests per year and the total number of positive cases in children further divided by vaccination status.

Abbreviations: AGE, acute gastroenteritis; RV, rotavirus,

great decrease in positive cases as in 2015, 2.9% (32/1108) followed by 1.1% (12/1108) in 2016 and just 0.4% (4/1108) in 2017.

3.1 | Prevalence of G and P types

Out of the 487 rotavirus antigen-positive samples, 438 (90%) were characterized according to both G and P types, while 49 (10%) could not be fully genotyped. Among the partially typed specimens, one of the genotypic specificities could be determined in 36 cases; G-type in 13 cases and P-type in 23 cases. Thirteen of the antigen-positive cases were nontypeable. The distribution of genotypes is presented in Table 1. Overall, the most frequently found G-types were G1, G9 and the most common P-types were P[8] (Table 1).

3.2 | Geographical distribution of rotavirus positive cases according to genotypes

The temporal and regional variation in rotavirus genotypes across the three geographical regions (south-east, west, central) from 2014 to 2018 can be seen in Figures 1 and 2, and Table 2, respectively. Most of the positive samples were detected in the period from January to May during all 5 years in the project period. Table 2 shows the total amount of positive cases per hospital and the total amount of specimens that were genotyped. The genotype distribution was similar in all geographical regions and type G1P[8] was the most frequent.

3.3 | Distribution of genotypes according to year, age group, and hospitalization

Table 3 provides an overview of the distribution of genotypes for children born within the years 2014–2018. Genotype G1P[8] was the most common type of rotavirus in 2014 before the introduction of the vaccine, accounting for 52,7% and remaining the most common type for birth cohorts in 2015 and 2016. The second most common type, G9P[8] was detected in 24.1% of cases born before the vaccine was implemented in 2014. In birth cohorts born after vaccine introduction, the number of positive samples decreased remarkably, and the various genotypes were

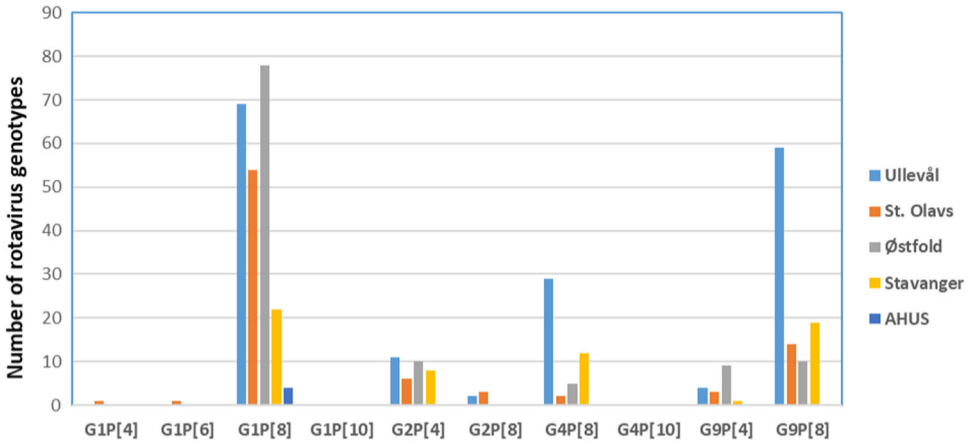

FIGURE 2 Rotavirus genotypes per hospital. G1P[8] was the most frequent genotype in all age groups followed by G9P[8] in all the participating hospitals

only sporadically found like was mentioned before. Mixed infection was only found in one case in 2014, where G1P[4]P[8] was detected.

Table 3 shows the breakdown of genotype results by age group and the age distribution of hospitalized cases. Overall, most cases were found in children between 12 and 24 months of age, and G1P[8] was the most frequent genotype in all age groups followed by G9P[8].

Out of the G1P[8] strains detected after vaccine implementation, 21.4% were identified as Rotarix vaccine strain.[11]

3.4 | Genotype according to the Vesikari scoring system

The Vesikari Clinical Severity Scoring System was used to assess the severity of rotavirus infections.[12] Most of the AGE cases were scored in the category moderate and severe, accounting for 18.4% and 80.2%, respectively. Only a few cases could be classified as mild (Table 4). The results from genotyping showed that type G1P[8] was the most frequent genotype followed by G9P[8] both in children with moderate and severe AGE. No differences in genotypes according to the severity score system by Vesikari were seen.

3.5 | Correlation between genotype results from the bulk stool and rectal swabs

Paired bulk stool and rectal swab samples from 77 cases were successfully genotyped. In 72 cases (93.5%) of the paired samples, a correlation of genotyping was found between bulk stool and rectal swabs. In 5 cases (6.5%) genotyping was unsuccessful in the rectal swabs, most likely due to a low level of virus (Table 5).

4 | DISCUSSION

This study showed a substantial reduction in the number of positive rotavirus cases admitted to the hospital after the implementation of vaccination in Norwegian infants in 2014. The decrease in cases was seen across all age groups. The results are in line with earlier findings.[13]

We observed a marked seasonality during the study period, with most of the rotavirus positive cases found during the winter and spring months, which is in accordance with previous reports.[3,13]

After the rotavirus vaccine introduction, 21.4% of the specimens were positive for the Rotarix vaccine strain.[11] Similarly, rotavirus vaccine strain shedding was found in 18.8% of specimens from surveillance in other countries with Rotarix vaccine in childhood vaccination programs.[14,15] Also, in the period from 2015 to 2018, 27.2% of the positive rotavirus samples detected in routine testing at St. Olav's hospital were vaccine strains which correspond with results in this study (personal communication Svein Arne Nordbø). These results are in contrast to a Japanese study that found that only 1.6% of the positive specimens contained the Rotarix vaccine virus.[16] Variations between countries depend on many factors, where some of the most important include the age of the study population, inclusion criteria, detection methods, and vaccination coverage. The majority of infants shed vaccine virus up to 14 days after the first Rotarix dose resulting in antigen and PCR positive test results.[17] The only way to distinguish between a vaccine strain and a wild-type virus is by PCR-based genotyping or relevant sequencing method, which is important in rotavirus surveillance, but also in individual case investigation or outbreaks.

Our study showed no geographical or temporal difference in genotype predominance. No clear changes in the distribution of genotypes were observed in the postvaccine years 2015–2018. Some other European countries such as the United Kingdom and Belgium reported an increase in the prevalence of G2P[4] strains immediately after the start of rotavirus vaccination but later a

TABLE 2 Distribution of rotavirus genotypes during the project period from 2014 to 2018

	Strains with detected genotype according to year of birth									
	2014		2015		2016		2017		2018	
Genotype	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Single infections										
G1P[4]	1	0.2	0	0	0	0	0	0	0	0
G1P[8]	212	52.3	8	44.4	5	55.6	1	16.7	0	0
G1P[10]	0	0	0	0	0	0	1	16.7	0	0
G2P[4]	31	7.6	2	11.1	1	11.1	1	16.7	0	0
G2P[8]	4	1.0	0	0	0	0	1	16.7	0	0
G4P[8]	46	11.3	1	5.5	0	0	0	0	0	0
G9P[4]	11	2.7	3	16.6	2	22.2	1	16.7	0	0
G9P[8]	97	23.9	3	16.6	1	11.1	1	16.7	0	0
Other	3	0.7	1	5.5	0	0	0	0	0	0
Total	405		18		9		6		0	
Mixed infections										
G1P[4]P[8]	1	100	0	0	0	0	0	0	0	0
Partly typed strains										
G1	11	37.9	3	50.0	1	33.3	2	100	0	0
G2	0	0	1	16.7	2	66.7	0	0.0	0	0
G4	1	3.4	1	16.7	0	0.0	0	0.0	0	0
G9	12	41.4	1	16.7	0	0.0	0	0.0	0	0
G1G2	0	0	0	0.0	0	0.0	0	0.0	0	0
Other	5	17.2	0	0.0	0	0.0	0	0.0	0	0
Total	29		6		3		2		0	
P4	4	13.3	1	14.3	1	33.3	0	0.0	0	0
P6	2	6.7	1	14.3	0	0.0	1	100.0	0	0
P8	20	66.7	5	71.4	2	66.7	0	0.0	0	0
P[8]P[10]	0	0	0	0.0	0	0.0	0	0.0	0	0
Other	4	13.3	0	0.0	0	0.0	0	0.0	0	0
Total	30		7		3		1		0	
VP7 and VP4 genotyping										
G1	222	48.2	13	43.3	6	37.5	3	37.5	0	0
G2	38	8.2	3	10.0	3	18.8	2	25.0	0	0
G4	53	11.5	3	10.0	2	12.5	1	12.5	0	0
G9	122	26.5	6	20.0	3	18.8	2	25.0	0	0
G1G2	1	0.2	0	0	0	0	0	0	0	0
Total	461		30		16		8		0	
P4	51	11.0	7	23.3	4	25.0	3	42.9	0	0
P6	10	2.2	1	3.3	0	0	1	14.3	0	0
P8	397	85.6	22	73.3	10	63.0	3	42.9	0	0
Total	464		30		16		7		0	

fluctuation in the prevalence happened and other types became more prevalent resulting in a mixed picture.[18,19] In a recent review of genotypes circulating after rotavirus vaccination in various countries, no distinct pattern was found related to Rotarix vaccine use.[6] The genotype diversity varied from year to year regardless of the implementation of a vaccination program most probably due to natural variation over time in strain distribution. Nevertheless, continued rotavirus surveillance is vital to detect any changes in strain prevalence associated with vaccine use.

One limitation of our study is that the majority of the cases were hospitalized children with severe AGE. Our results might, therefore, not be applicable to mild nonhospitalized AGE occurring in the community. Another limitation is the low number of cases included during the last year in the project period allowing for fewer samples to be genotyped. After vaccine implementation, the number of AGE cases admitted to hospitals dropped dramatically. The same pattern regarding annual case numbers and genotype distribution was seen in the surveillance at the national reference laboratory, which supports our findings in this study.

We have previously shown that rectal swabs are suitable and can be used for the detection of rotavirus when bulk stool is difficult to acquire and that the EIA method has the same high sensitivity of 95% for detection of RV strains compared to the molecular method making it suitable for screening.[20] The present study investigated the appropriateness of rectal swabs for genotyping compared to bulk stool and the correlation was high. These findings support the use of rectal swabs as a convenient and easily accessible specimen type in a rotavirus surveillance program for follow-up on the effects of a vaccine introduction.

In countries where vaccination is implemented, it is not known if and how this may impact the rotavirus disease burden in non-vaccinated older children and adults. Elderly living in institutions are at risk of contracting rotavirus as outbreaks often occur in such health care settings. Therefore, it is important to have a special focus on this vulnerable group and conduct surveillance of prevalence and circulating genotypes also in the adult and elderly population.

In the near future, methods to detect and differentiate wild-type RV strains, as well as vaccine strains by Next-Generation Sequencing, will be needed to investigate potential vaccine escape mutants.

In conclusion, continuous rotavirus genotype surveillance is crucial for assessing the effectiveness of a vaccine program and monitoring for any emergence of vaccine-escape strains. Genotyping is also necessary for the detection of vaccine strains in newly vaccinated cases. It is important for clinicians to be aware that recently vaccinated infants can shed the vaccine strain thereby resulting in falsely positive tests.

TABLE 3 Rotavirus genotype distribution per hospital

Hospital vs genotyping					
Genotyping	**Ullevål**	**St. Olavs**	**Østfold**	**Stavanger**	**AHUS[a]**
G1P[4]	0	1	0	0	0
G1P[6]	0	1	0	0	0
G1P[8]	69	54	78	22	4
G2P[4]	11	6	10	8	0
G2P[8]	2	3	0	0	0
G4P[8]	29	2	5	12	0
G9P[4]	4	3	9	1	0
G9P[8]	59	14	10	19	0
Total	174	84	112	62	4

[a]Few cases are reported from AHUS hospital due to the study period starting later than the other hospitals.

TABLE 4 Rotavirus genotype and hospitalization by age group

No. and % of strains for children according to months of age												
Genotype or hospitalization status	**Total**		**<12**		**12–24**		**24–36**		**36–48**		**48–59**	
Genotype	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
G1P[4]	1	0.2	0	0	1	0.5	0	0	0	0	0	**0**
G1P[8]	227	43.9	58	38.1	110	53.4	40	40	13	40.6	6	23.1
G2P[4]	35	6.8	10	6.6	9	4.4	8	8	3	9.4	5	19.2
G4P[8]	48	9.3	10	6.6	22	10.7	12	12	3	9.4	1	3.8
G9P[8]	102	19.7	36	23.7	43	20.9	16	16	3	9.4	4	15.4
Other	104	20.1	38	25.0	21	10.2	24	24.0	10	31.6	11	42.3
Total	517		152		206		100		32		26	
Hospitalized	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Yes	439	85.0	125	82.2	174	84.5	91	91	27	84.4	22	84.6
No	77	15.0	27	17.8	32	15.5	9	9.0	5	15.6	4	15.4
Total	516		152		206		100		32		26	

TABLE 5 Genotype distribution according to the severity of rotavirus gastroenteritis by the Vesikari scoring system

	Mild <7		Moderate 7–10		Severe ≥11	
Genotype	*n*	%	*n*	%	*n*	%
G1P[4]	0	0.0	1	1.5	0	0.0
G1P[8]	3	60.0	32	48.4	144	50.1
G2P[4]	1	20.0	7	10.6	22	7.6
G2P[8]	0	0.0	1	1.5	3	1.0
G4P[8]	0	0.0	9	13.6	34	11.8
G9P[4]	0	0.0	4	6.0	10	3.48
G9P[8]	1	20.0	12	18.1	74	25.7
Total	**5**	1.4	66	18.4	287	80.2

ACKNOWLEDGMENTS

We would like to acknowledge the staff of all hospitals participating in the Norwegian Enhanced Pediatric Immunization Surveillance network (NorEPIS). We also thank NorEPIS project coordinator Terese Bekkevold, and all enrolled children and their families for their valuable contribution to this study.

FUNDING INFORMATION

The Norwegian Institute of Public Health provided the financial and other resources for the implementation of this study.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Susanne Gjeruldsen Dudman, Elmira Flem, and Moustafa Gibory: contributed to the design and implementation of the study. **Moustafa Gibory, Ildri Haltbakk, and Jennifer Lynn Dembinski**: performed the lab analysis. **Susanne Gjeruldsen Dudman, Elmira Flem, Jennifer Lynn Dembinski, and Moustafa Gibory**: contributed to the data analysis and interpretation. All authors discussed the results and commented on the manuscript. All the authors reviewed and approved the final manuscript to be published.

ETHICS STATEMENT

The Regional Committees for Medical and Health Research Ethics (REK) approved this study. Written informed consent was obtained from parents or legal guardians of all included children.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available at the Norwegian Institute of Public Health NIPH upon request.

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How to cite this article: Gibory M, Bruun T, Flem E, et al. Genetic diversity of rotavirus strains circulating in Norway before and after the introduction of rotavirus vaccination in children. *J Med Virol*. 2021;1-8. doi:10.1002/jmv.27484