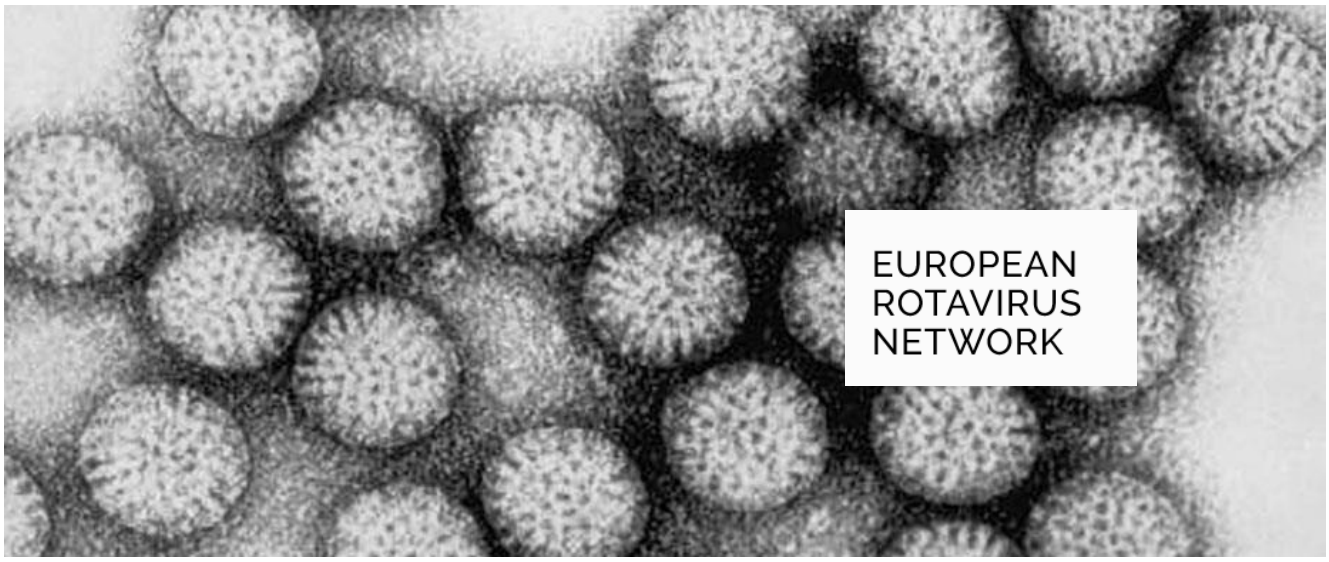

EUROROTANET

ANNUAL REPORT 2020

About EuroRotaNet

EuroRotaNet surveillance network was established in 2007 to conduct rotavirus strain type surveillance in Europe.

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Executive Summary

- Of the total 74,899 rotavirus positive samples characterized between 2006 and 2020, 94% contained a single rotavirus strain. Strain mixtures of partially typed strains represented 6% of samples.
- In 2019/20 there were 1352 samples typed and data were submitted to EuroRotaNet from 12 countries. This compares to a mean of 5657 per year for the previous 13 seasons. This reduction in samples typed is a consequence of the global COVID-19 pandemic.
- In 2019/20, 32% of typed samples were from the UK. Austria, Denmark, Germany and Slovenia submitted fewer samples than the World Health Organization recommended, 50-60 samples for typing. Therefore, genotype distributions in these countries in 2019/20 should be interpreted with caution.
- In 2019/20, 9 genotypes circulated with a prevalence > 1%: G1P[8], G2P[4], G9P[8], G3P[8], G12P[8], G8P[8], G3P[4], G8P[14] and G9P[4]. Genotype diversity varied by country but G3P[8] was the most prevalent genotype, detected in 22% (n=274/1236) of single type samples. The majority of these detections were in samples from France (49%). Single strain type dominance has been rarer in recent years and there has been an increase in the relative proportion of less common genotypes.
- Up until 2015/16 G1P[8] rotaviruses were the most prevalent year on year, ranging from 31% (2014/15) to 62% (2007/08) of single type strains typed. In 2019/20 the proportion of G1P[8] strains remained low and were only identified in 10% (n=122/1236) of single typed samples.
- In the UK in 2019/20 the proportion of G1P[8] single type specimens detected remained low. In Sweden, where a pilot of rotavirus vaccination was introduced in 2014 and expanded to the national immunisation schedule in 2019, the proportion of G1P[8] detections has decreased steadily from 2011/12, detected at a nadir of 3% of single typed samples in 2018/19 and was only detected in 6/62 samples in 2019/20.
- During 2019/20: G12P[8] remained dominant in Italy, accounting for 42% of single typed strains. Whilst in Finland G9P[8] was predominant (52%) and G3P[8] dominated in France (50%).
- There has been no significant number of novel emerging strains detected.
- There is no evidence to date that rotavirus vaccination programs are driving the emergence of rotavirus vaccine escape strains. Differences in the relative distribution of strains in the post-vaccine era should be interpreted within the context of the natural changes in diversity seen in association with age and seasonality in countries prior to vaccine introduction or without rotavirus vaccination.
- In the UK, a large number of vaccine-derived strains were detected post-vaccine introduction in infants <6 months of age. Detections in infants < 6 months of age with gastrointestinal symptoms coincides with the Rotarix™ vaccine schedule; they are likely shedding vaccine strain post-vaccination with symptoms possibly caused by other infectious or non-infectious aetiologies.

Background

The European Rotavirus Network, EuroRotaNet, was established in January 2007. EuroRotaNet network has conducted rotavirus strain surveillance in Europe for 14 consecutive years including data since September 2006. Participation in the EuroRotaNet is voluntary, and the network activities are funded between the collaborating institutes, GlaxoSmithKline Biologicals (GSK) and Sanofi Pasteur-MSD (SPMSD), and after the closure of SPMSD in December 2016 by Merck Sharp & Dohme (MSD).

EuroRotaNet was established to gather comprehensive information of the rotavirus types co-circulating throughout Europe, encompassing rotavirus seasons pre- and post- vaccine introduction.

The aims of the study are to:

- Develop and apply methods and algorithms for effective rotavirus typing (G and P) and characterisation (and inform and conduct additional characterization through gene specific or whole genome sequencing as necessary).
- Monitor the effectiveness of genotyping methods and respond to changes associated with genetic drift and shift.
- Describe in detail the molecular epidemiology of rotavirus infections in Europe, during consecutive rotavirus seasons, through genotyping of rotavirus-positive samples.
- Monitor the emergence and spread of common and novel rotavirus strains within Europe.
- Develop the infrastructure that may serve as a platform for additional surveillance activities and nested studies for evaluating the effectiveness of a rotavirus vaccine in the general population, through monitoring the reduction in disease associated with common rotavirus types; the possible vaccine-induced emergence of antibody escape mutants; the possible emergence in the general population of genotypes other than those included in the vaccine; and the possible emergence in the general population of reassortants between vaccine and naturally circulating wild-type strains.

Current membership of EuroRotaNet includes 13 European countries. Denmark, Finland, France, Germany, Hungary, Italy, Slovenia, Spain, Sweden and the United Kingdom joined in 2007. Belgium in January 2008, Greece in January 2009 and Austria in December 2010. Bulgaria and Lithuania were members of EuroRotaNet from January 2008 until August 2013 and The Netherlands from 2007 to August 2017. Hungary is not included in the annual reports between 2017/18 and 2019/20 as data was not available to the network. Data for these countries can be found in previous annual reports.

For further background information about EuroRotaNet please visit our website http://www.eurorotanet.com

Vaccination

Two rotavirus vaccines have been licensed for use since 2006 in Europe, the single strain, human-derived live-attenuated human two-dose oral vaccine (Rotarix™, GlaxoSmithKline Biologicals, Belgium) and the live human-bovine reassortant three-dose vaccine (RotaTeq™, Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey, U.S.A).

Vaccine coverage is variable across EuroRotaNet countries. In Belgium (predominately using Rotarix™), Austria (changed between Rotarix™ and RotaTeq™ tenders), Finland (exclusively using RotaTeq™) and the United Kingdom (exclusively Rotarix™) rotavirus vaccination was introduced into national immunisation programmes in 2006, 2007, 2009 and 2013 respectively. Recent figures suggest these countries all have vaccine uptake of over 90% (1–3).

Countries which have more recently introduced rotavirus vaccination nationally include Germany and Sweden. In Germany routine rotavirus vaccination has been recommended by regional health authorities since 2008 but coverage was moderate for a number of years, as rotavirus vaccine was only available through health insurance in some states, and state based coverage ranged from 11% to 77% (1,4). However, since 2013 the vaccine has been recommended nationally (both vaccines available), with vaccine coverage increasing to 80% in 2018 (5). In Sweden in 2014 rotavirus vaccination was introduced into the childhood immunisation schedule of some regions as part of a pilot scheme, for instance, in Stockholm County (6) and since September 2017 vaccination was recommended for all regions (7). It was introduced universally into the national immunisation programme in September 2019, with Rotarix™ being used. The official country reported coverage for Sweden in 2019 and 2020 was >80% (3,8,9).

A number of other countries have variable access to rotavirus vaccines. In Greece vaccination is permissively recommended with 75% funding and the vaccine coverage estimated at ~20% (3,7,10,11). In Slovenia, vaccination began on a voluntary basis in 2007 with Rotarix™, with RotaTeq™ also available from 2008. Coverage in 0-1 year olds reached 27% in 2009 but has slowly decreased since (12).In Spain vaccination is not included in the routine childhood immunisation schedule, but is recommended for all infants by the Spanish Association of Pediatrics (13). Vaccination is available privately (from 2010 to 2016 only RotaTeq™ was available on the Spanish market) but vaccine coverage is currently highly variable by region (ranging from~10% to ~70%) (1,14,15). In Italy rotavirus vaccination has been recommended at a subnational level since 2013 but recommended nationally since 2017 vaccine coverage was estimated to be 19% in 2018 and 61% in 2019 but remains highly variable by region (1,3,16,17). In Denmark, France and Hungary there remains no governmental recommendation for rotavirus vaccination (7).

EuroRotaNet Data Analysis

Genotyping data

Study samples included rotavirus-positive faecal samples submitted for routine laboratory diagnostic testing from sporadic cases of gastroenteritis, who attended primary care, accessed emergency services or were hospitalized. Samples were typed in each participating country using standardised G and P typing methods. In the post-vaccine era the UK, Germany and Finland have regularly been able to identify vaccine-derived strains and more recently Austria and Spain. Rotarix™ vaccine-derived strains were defined on the basis of the sequences of the VP4 and VP7 encoding genes displaying highest homology with Rotarix™ sequences and/or, through the detection of the Rotarix™ strain NSP2-using a published and validated qRT-PCR assay (18). RotaTeq™ vaccine derived strains were defined by the sequences of the VP6 encoding genes to determine bovine origin (19,20). In addition to the binary classification system based on G and P types, rotavirus strains are often classified into genotype-constellations based on a common genomic backbone. Human rotaviruses typically belong to the Wa-like or the DS-1-like genotype-constellations and such classification will also be referred to in this report.

The sample size for the number of rotavirus positive samples typed was calculated based on detecting genotypes with prevalence ≥1% based on pre-vaccine data. This is dependent upon the country population size and is therefore not representative of the incidence of rotavirus gastroenteritis (21). Currently, the World Health Organization recommends a minimum of 50-60 randomly selected rotavirus positive samples for genotyping per year per country (22). Furthermore, sample size calculations are only valid for countries without routine rotavirus vaccination, as countries with vaccination may not be able to reach this target. In some post-vaccine years we have seen an increase in the number of samples genotyped in Finland and the UK; countries with routine vaccination. However, this should not be interpreted as an increase in rotavirus disease incidence as the network is not powered or designed to assess rotavirus disease burden. It is most likely that the increase is the result of better coordinated national surveillance.

It is likely that in the 2019/20 season non-pharmaceutical interventions intended to reduce COVID-19 transmission have also significantly contributed to reducing the transmission of rotavirus (23). In addition access to health care and laboratory testing could have further contributed to the observed reductions, and these two factors combined resulted in fewer rotavirus samples available for typing for EuroRotaNet laboratories.

Epidemiological data

Epidemiological data include the variables in Table 1, overleaf. Data on setting, symptoms, and geographical location have variable completion and there is no standardized definition for these variables across EuroRotaNet countries. Therefore, analyses of these data items have not been included in this report. Furthermore, testing and diagnosis of other co-infections is not collected. In 2019/20 the UK did not submit any data for sex, geographical region, setting, area type or symptoms. In 2019/20 Italy, Greece, Spain and Finland submitted data on rotavirus vaccine status. For Spain this was submitted for 11% of samples, 12% for Finland 28% for Italy and 100% for Greece. Further analysis of these data can be found later in this report.

Table 1. Epidemiological data items and level of completion

Variable	Detail	% Completion (Country Range)
		Sept 2019 to Aug 2020
Age	Age in months and years	99.9% (91-100%)
Sex	Male, Female or Unknown	65% (0-100%)
Geographical region	Country specific geographical regions	52% (0-100%)
Setting	Hospital or Community	52% (0-100%))
Area type	Urban or Rural	26% (0-100%)
Symptoms	Diarrhoea, vomiting, or diarrhoea and vomiting, or other	24% (0-100%)
Vaccination status	Number of doses and vaccine used	10% (0-100%)

Molecular Epidemiology Rotavirus Infections in Europe, 2006-2020

Data from a total of 74,899 rotavirus-positive samples collected between September 2006 and August 2020 in a total of 12/13 collaborating European countries were uploaded to the EuroRotaNet database (Table 2). For practical reasons, a rotavirus season was defined as the 12 months between September and August of the following calendar year.

Between the period 2006/07 and 2018/19 there were between 3065 and 6954 samples typed per year across the 12 EuroRotaNet countries, with a mean of 5657. France, Italy and the UK contributed a mean of 932, 890 and 1053 typed samples per year.

Table 2. Number of rotavirus strains in the EuroRotaNet database per country and rotavirus season, between September 2006 and August 2020

Country	06/07	07/08	08/09	09/10	10/11	11/12	12/13	13/14	14/15	15/16	16/17	17/18	18/19	19/20	Total
Austria	NA	NA	NA	NA	289	190	114	202	67	114	244	138	173	33	1564
Belgium	NA	610	413	381	527	281	373	239	623	278	482	323	482*	84	5096
Denmark	185	277	260	318	225	231	190	196	210	81	179	108	245	11	2716
Finland	142	266	227	52	98	58	77	187	203	112	209	331	188	114	2264
France	578	766	810	923	909	880	1196	1259	1225	1059	946*	831*	734*	290	12406
Germany	40	964	752	736	368	463	269	43	148	198	424	151	318	14	4888
Greece	NA	NA	380	384	366	507	229	420	270	287	230	176	232	104	3585
Italy	346	1290	753	1379	1121	1305	1118	1142	819	737	781	406	381	94	11672
Slovenia	353	631	468	436	473	494	394	513	528	314	280	46	176	31	5137
Spain	544	662	537	616	824	1479	495	748	604	543	579	563	589	81	8864
Sweden	32	578	115	109	111	150	169	258	200	203	234	207	152	62	2580
UK	845	910	975	877	681	792	1075	673	1289	770	1763*	1084	1959*	434	14127
Total	3065	6954	5690	6211	5992	6830	5699	5880	6186	4696	6351*	4364*	5629*	1352	74899

NA country not part of the network. Post vaccine period is shown in blue for those countries with national programmes.

*: Updated figures compared to previous reports as countries submitted historic samples which were typed in 2019/20 to EuroRotaNet.

In the 2019/20 season the number of samples typed were substantially reduced across all countries compared to previous seasons (Table 2). There were only 1352 samples typed and submitted to EuroRotaNet, with 32% of these from the UK. Austria, Denmark, Germany and Slovenia were unable to submit the WHO recommended minimum number of 50-60 random samples for typing.

This reduction is likely an effect of the COVID-19 pandemic on rotavirus case rates across Europe (24). COVID-19 public health measures and reduced social interactions will have reduced transmission of endemic seasonal diseases, such as rotavirus during 2020. Furthermore, there would have been changes in healthcare seeking behavior, rotavirus testing capacity and testing algorithms as a result of the pandemic, which is likely to further have reduced the number of rotavirus positive samples available for typing. For, example laboratory reports of rotavirus positive detections in 2020 in the UK were unusually low (sensitive: Public Health England data not shown).

Rotavirus infections predominantly occur in the winter and spring months in temperate climates, and the analysis of the data in EuroRotaNet, although not intended to measure the incidence of rotavirus disease, does reflect this seasonality. Between 2010 and 2019 the average peak of rotavirus infections occurred in March (Figure 1).

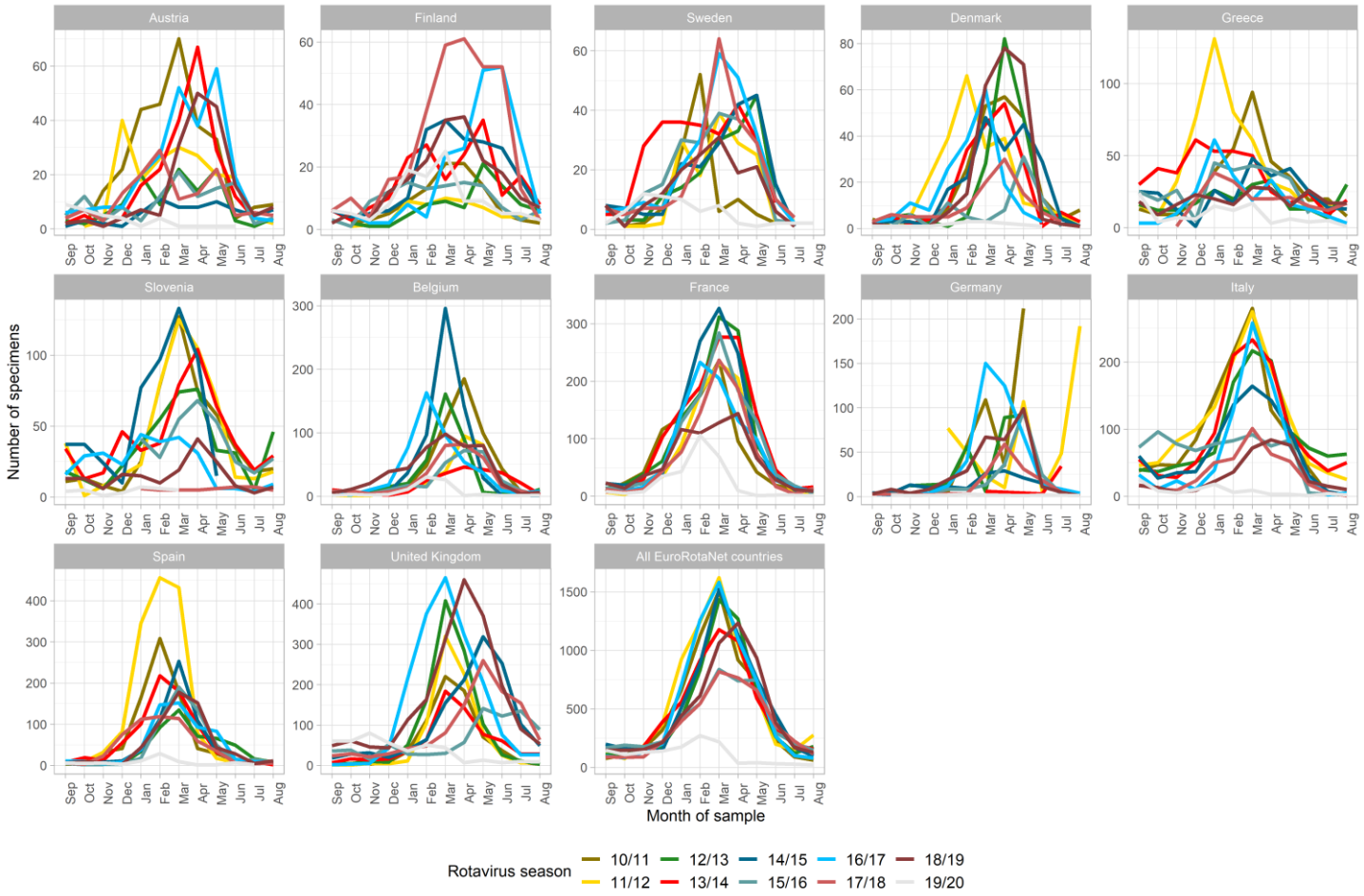

Figure 1. Temporal distribution of typed rotavirus specimens by country, September 2010 to August 2020 (data only shown for last 10 years; y axes vary for each country)

In the 2019/20 season peak rotavirus detections were very variable between countries with the season being earlier than March in most coutries. Crucially, there were only 159/1352 (12%) samples post-March in 2020, in previous years the proportion of samples from April to August ranged between 30% and 50%. However, due to a combination of the low number of samples submitted to EuroRotaNet from a number of countries, and without access to incidence data and total samples tested, interpreting these finding is challenging.

Prior to 2019/20 differences were observed across the EuroRotaNet participating countries in the month in which rotavirus infections peaked. Year on year, the earliest peaks of infection were detected in Spain in late winter / early spring, although a trend towards a delay in the peak of infection has been seen in the period 2018/2019. Peaks of infections occur typically in the spring in the north and eastern European countries (April-May) (see Figure 1). These data confirms the previously reported trend that rotavirus infections spread in Europe from South to North and West to East, similar to the pattern of spread described for the USA. (21,25,26)

Genotype Distribution

Of the total 74,899 samples characterised, 70,638 (94.3%) contained a single rotavirus strain (Table 3). Strain mixtures, or partially typed strains represented 5.7% of samples. Single types were identified in nearly 100% of samples in Belgium. In 2019/20 the proportion of mixed or partially typed strains was higher than previous years (n=116; 8.6%) and was highest in Spain (n=15; 18.5%). The primary aim of EuroRotaNet is to characterise rotavirus strains across the European region and provide data on strain diversity with an agreed cut-off prevalence of ≥1%.

Table 3. Distribution of infections with single rotavirus strains, multiple strains or with partially genotyped strains in rotavirus seasons, between September 2006 and August 2020.

Country	Single (N)	(%)	Mixed/partially typed (N)	(%)	Total (N)
Austria	1375	87.9	189	12.1	1564
Belgium	5089	99.9	7	0.1	5096
Denmark	2474	91.1	242	8.9	2716
Finland	2170	95.8	94	4.2	2264
France	11779	94.9	627	5.1	12406
Germany	4817	98.5	71	1.5	4888
Greece	3440	96.0	145	4	3585
Italy	10221	87.6	1451	12.4	11672
Slovenia	4972	96.8	165	3.2	5137
Spain	8264	93.2	600	6.8	8864
Sweden	2480	96.1	100	3.9	2580
United Kingdom	13557	96.0	570	4	14127
Total	70638	94.3	4261	5.7	74899

Overall, 7 genotypes circulated with a prevalence ≥1% and included G1P[8], G4P[8], G2P[4], G9P[8], G3P[8], G12P[8], and G9P[4]. These 7 genotypes made up 91% of all characterised strains, and 96% of all cases in which a single rotavirus strain was identified. The remaining 49 single G and P type combinations represented 3% of the total typed specimens. G1P[8] rotaviruses were the most prevalent year on year between 2006/07 and 2014/15, ranging from 31% in 2014/15 to 62% in 2007/08 (Table 4). In 2015/16, for the first time since EuroRotaNet started collecting data, a strain type other than G1P[8] dominated, and G9P[8] was found in 34% of single strain infections characterised. The increase in G9P[8] occurred in both, countries with and without routine rotavirus vaccination.

In 2019/20, 9 genotypes circulated with a prevalence > 1%: G1P[8], G2P[4], G9P[8], G3P[8], G12P[8], G8P[8], G3P[4], G8P[14] and G9P[4]. The remaining 22 single G and P type combinations represented 6% of single typed specimens. In 2019/20 G3P[8] was the most detected genotype (22%), with the majority of these detections from France (49%; 134). In 2019/20 G1P[8] was only detected in 10% (n=122) of single typed specimens.

Table 4. Most common genotypes found in single rotavirus strain infections (>=1%), by rotavirus season, between September 2006 and August 2020

Genotype	06/07 (%)	07/08 (%)	08/09 (%)	09/10 (%)	10/11 (%)	11/12 (%)	12/13 (%)	13/14 (%)	14/15 (%)	15/16 (%)	16/17 (%)	17/18 (%)	18/19 (%)	19/20 (%)	Total (%)*
G1P[8]	1484	4029	2356	3072	3041	2709	2286	2114	1870	671	470	465	504	122	25193
	(53)	(62)	(44)	(52)	(54)	(42)	(42)	(38)	(31)	(15)	(8)	(11)	(9)	(10)	(36)
G9P[8]	623	768	571	751	443	847	807	918	1246	1511	1600	788	1153	159	12185
	(22)	(12)	(11)	(13)	(8)	(13)	(15)	(17)	(21)	(34)	(27)	(19)	(22)	(13)	(17)
G2P[4]	337	578	604	732	737	951	996	820	735	791	2123	506	980	144	11034
	(12)	(9)	(11)	(12)	(13)	(15)	(19)	(15)	(12)	(18)	(35)	(12)	(18)	(12)	(16)
G3P[8]	113	292	358	152	429	494	601	636	536	395	847	1252	1352	274	7731
	(4)	(4)	(7)	(3)	(8)	(8)	(11)	(11)	(9)	(9)	(14)	(30)	(25)	(22)	(11)
G4P[8]	156	697	1175	937	660	792	410	738	829	355	251	145	101	7	7253
	(6)	(11)	(22)	(16)	(12)	(12)	(8)	(13)	(14)	(8)	(4)	(4)	(2)	(1)	(10)
G12P[8]	20	37	41	46	207	543	198	175	622	580	423	458	251	133	3734
	(1)	(1)	(1)	(1)	(4)	(8)	(4)	(3)	(10)	(13)	(7)	(11)	(5)	(11)	(5)
G8P[8]	2	1	6	0	6	0	2	7	3	35	34	15	386	19	516
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(0)	(7)	(2)	(1)
G9P[4]	4	13	17	21	16	5	8	5	21	26	103	279	284	77	879
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(2)	(7)	(5)	(6)	(1)
Total	2798	6519	5311	5888	5602	6425	5382	5532	5983	4487	6035	4115	5325	1236	70638
	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)

Denominator excludes mixed and partially typed strains.

*Percentages reported in brackets have been rounded to the nearest integer.

Since the introduction of routine vaccination in the UK and Germany the prevalence of G1P[8] has fallen consistently (Figure 2). In Germany between 2007/08 and 2012/13 the absolute number and proportion of rotavirus positive samples of infections caused by G1P[8] ranged from 123-405 and 23-47%, respectively. Since 2013/14 there has been a decline in the absolute number and proportion of infections caused by G1P[8], with just four detections in 2018/19 and one in 2019/20. In the UK alongside the decline in G1P[8] strains, there has been greater strain diversity and no one dominant strain post 2016/17, with variation season to season. This may reflect natural seasonal fluctuations and we cannot determine if there has been an absolute change in the number of infections caused by genotypes. Both the UK and Germany introduced rotavirus vaccination into their routine childhood immunisation schedules in 2013, with the exclusive use of the Rotarix™ vaccine in the UK and provider level choice of either RotaTeq™ or Rotarix™ in Germany.

Austria introduced vaccination in July 2007, and became part of EuroRotaNet in 2010. During this period the vaccine in use changed several times depending on tender procurement. Every year prior to 2014/15 G2P[4] had contributed over 60% of single strain infections and G1P[8] only caused 11% of infections on average. Since

2014/15 dominant strain types have changed year on year. In 2014/15 only 21% of samples submitted for typing were G2P[4], whilst G1P[8] was detected in 42% of samples. Since 2015/16, the dominant strain type has switched between G2P[4] and G3P[8]. In 2019/20 only 33 strains were typed and 42% of those were G2P[4]. It is unclear whether these shifts may be explained as natural fluctuations, age related sampling (most typed samples are from 55+ year olds) or whether changes in vaccine use may potentially have influenced strain distribution.

In Sweden prior to the 2012/13 season G1P[8] was the dominant genotype, it has since declined in dominance with greater strain diversity and variation in strain dominance seasonally. This decline in G1P[8] dominance seems to have occurred prior to pilot introduction of rotavirus vaccination in 2014. But G1P[8] has continued to decline as vaccination (with Rotarix™) was expanded to being recommended regionally from 2017/18 and then included in the national pediatric immunisation schedule from September 2019, with only 6/62 detections during 2019/20.

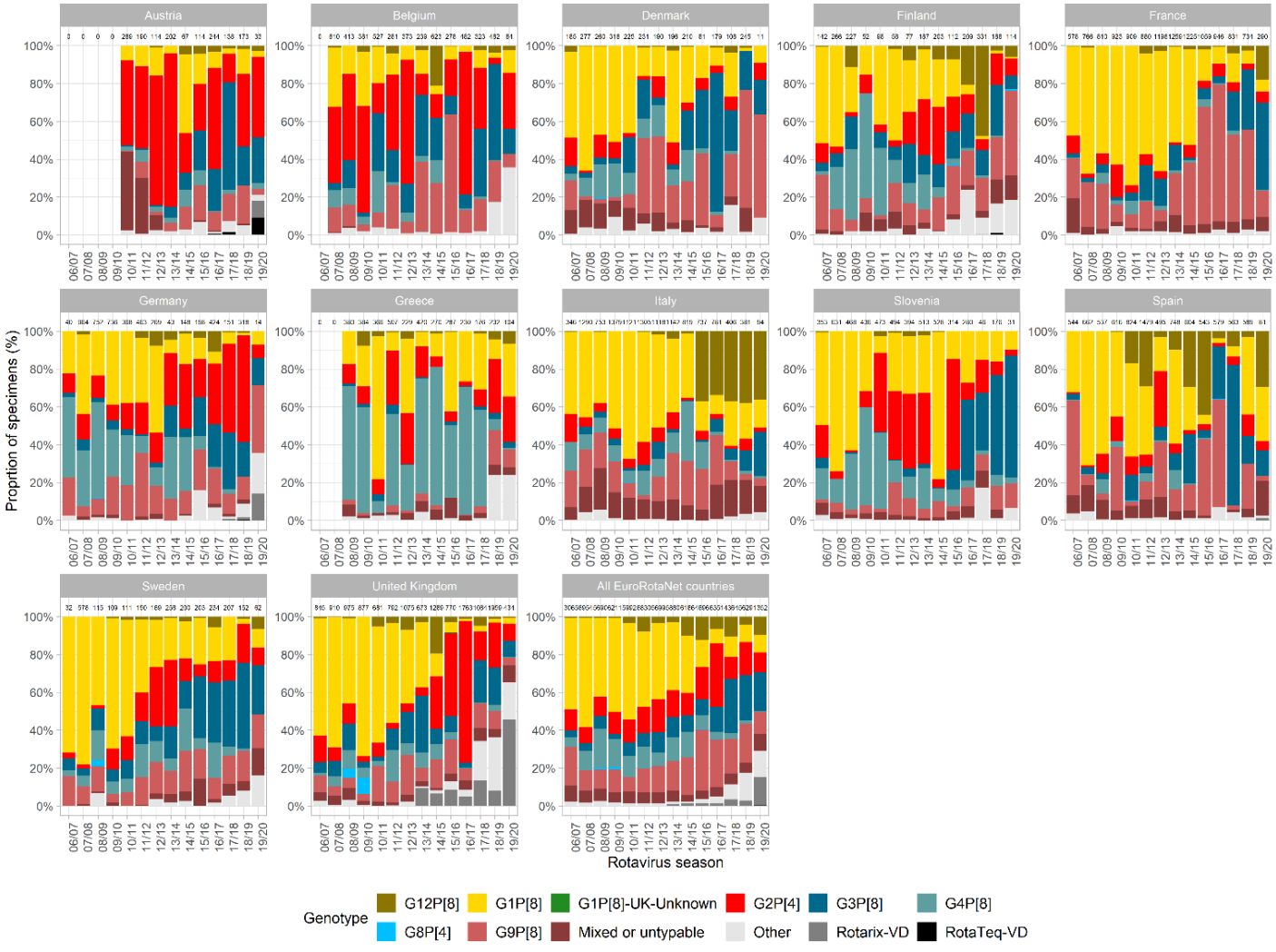

Figure 2. Temporal distribution of rotavirus genotypes, by country, between September 2006 and August 2020. *(VD= vaccine derived; total sample numbers are shown at the top of the stacked bars.)*

Elsewhere in 2019/2020 for single typed strains, G9P[8] dominated in Finland (52%), G3P[8] dominated in France (50%), whilst in Italy and Spain G12P[8] was most abundant (42% and 36%, respectively).

Although the reduction of G1P[8] strains over time seems to be universal across the EuroRotaNet countries, the proportion of G1P[8] strains is lower in those countries with universal rotavirus vaccination and high vaccine uptake (Finland, Austria, UK, Germany, Sweden and Belgium) compared to those without, across all age groups (Figure 3). The inverse can be seen for the relative proportion of G2P[4] strains.

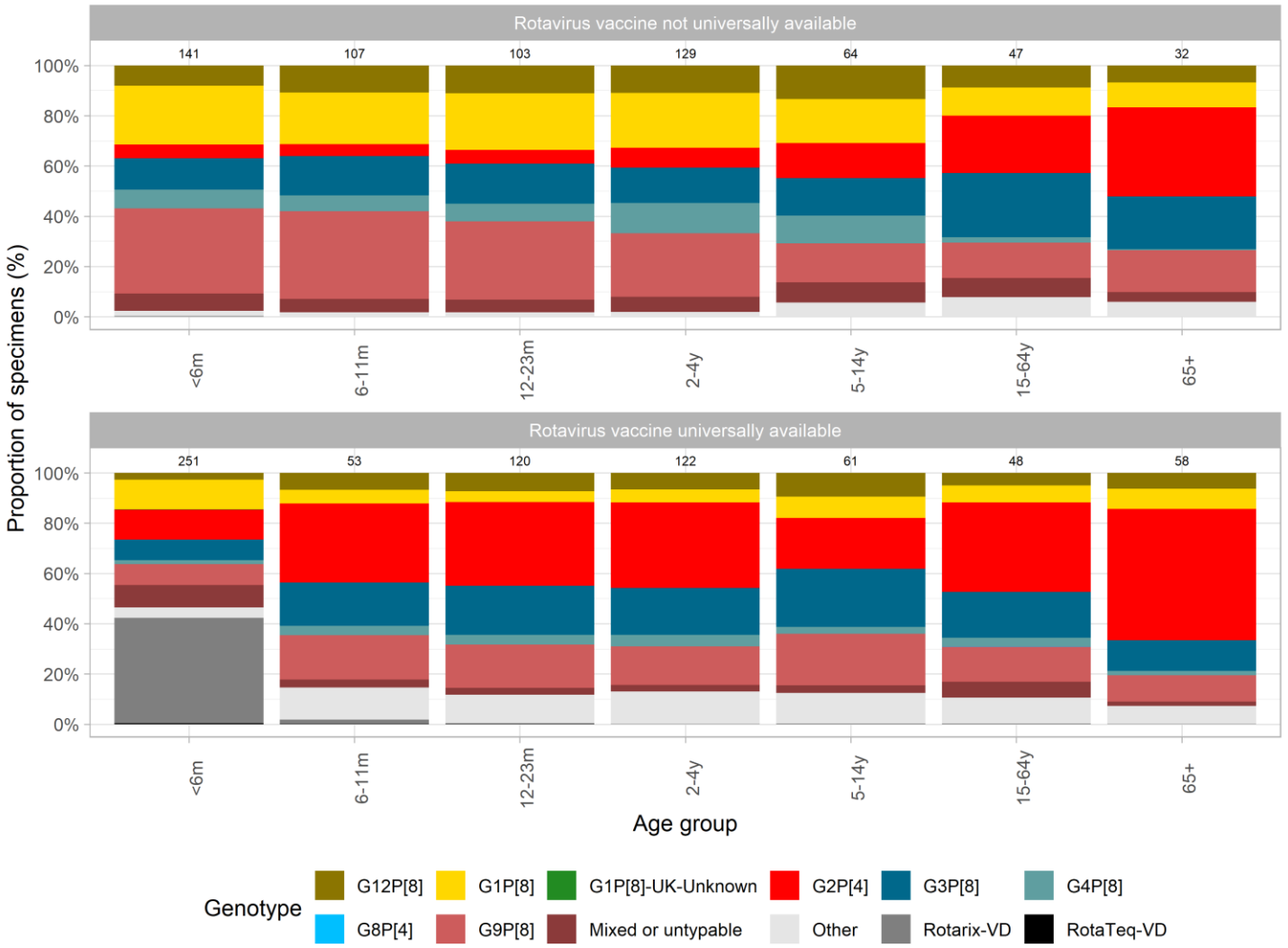

Figure 3: Rotavirus genotype distribution by age group in counties with universal vaccination compared to those without, between September 2014 to August 2020 *(VD= vaccine derived; excludes specimens where age was unknown total sample numbers are shown at the top of the stacked bars; countries with universal vaccination, include Finland, Austria, Belgium, Germany Sweden and the UK.)*

AGE OF INFECTION

Rotavirus infection in European children peaks among infants from 6 months to 2 years of age, but rotavirus infection can also be seen in older children and adults in those countries in which rotavirus is investigated as a cause of diarrhoea across all ages. As previously described, minor peaks in young adults and the elderly may possibly be associated with contact with infected children, waning immunity or the accidental detection of an (asymptomatic) rotavirus infection coinciding with infection by another gastrointestinal symptom-causing pathogen or other non-infectious aetiology (27,28). Interpretation of age of infection does need to take account of the aims of this study, which is rotavirus strain surveillance and not rotavirus disease incidence, and is likely to underestimate infections in older age groups as a whole.

In the UK where a large proportion of positive rotavirus samples are typed there has been a decline in the proportion and number of samples from infants <12 months of age since vaccine introduction in 2013 (excluding vaccine derived strains; Figure 4). In the pre-vaccine era 35% of samples were from infants <12 months, in 2019/20 it was 22%. In 2019/20 35% of samples came from children 2-4 years of age, compared to 18% in the pre-vaccine era. These 2-4 year olds would have been vaccine age eligible. However, further analysis is limited because data covering individual vaccine status has not been submitted to EuroRotaNet. Although fewer samples are typed in Germany and Sweden, since routine national vaccine introduction in 2013 in Germany and 2014 pilot vaccination in Sweden the proportion of samples from infants and children 12-23 months of age has declined.

Across all the countries studied between 2006/07 and 2019/20 G1P[8] strains contribute to 38% of single strain infections in the children <5 years (excluding vaccine derived strains) of age but only 14% in 65+ year olds. G1P[8] typically belongs to the genotype constellation 1 (Wa-like) and similar but less pronounced declines with increasing age are seen in the other strains from this genotype constellation (G3P[8], G4P[8], G9P[8] and G12P[8]). However, G2P[4] (genotype constellation 2 [DS-1-like]) follows a different distribution contributing only 14% in children <5 years of age but 29% in 15-64 year olds and 49% in 65+ year olds.

In 2019/20 G3P[8] was predominant among children<5 years (31%) and G9P[8] in 15-64 year olds (25%). However, in adults aged 65+ years G9P[8] and G2P[4] were predominant (30% and 27%, respectively) (Figure 5). In the UK the diversity of rotavirus strains detected among children aged 6-59 months of age has increased, mirroring the wider diversity detected in older children and adults (29).

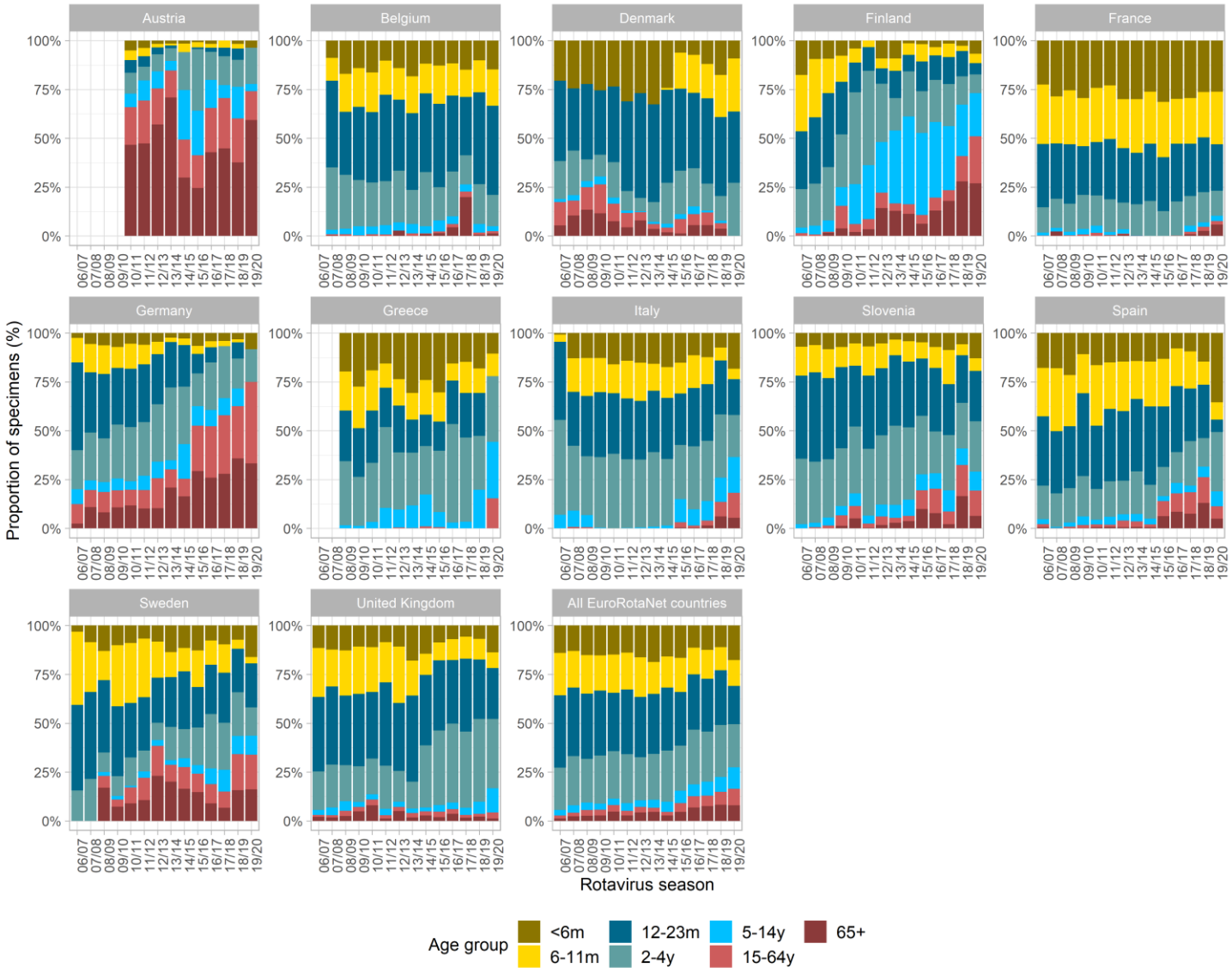

Figure 4. Age of infection by year, between September 2006 and August 2020 (*Vaccine-derived strains excluded*)

Figure 5. Genotype of typed specimens by age of infection and Country, between September 2019 and August 2020

(VD= vaccine derived; excludes specimens where case age was unknown total sample numbers are shown at the top of the stacked bars.)

Emerging Rotavirus Strains

Rotavirus strains emerging or remerging in Europe between 2006 and 2020 included G8P[8], G8P[4], G12P[8], G9P[4] and equine G3P[8] strains. Analysis of the different patterns of emergence for G8P[4], G3P[8] and G12P[8] strains has already been published and included in previous EuroRotaNet reports (available at https://www.eurorotanet.com/) (17,25,30–34). Over the past 14 years G3P[8] and G12P[8] have become well established in the EuroRotaNet network of countries. In 2019/20, Finland, Italy and France reported equine-like G3P[8] strain detections, with France reporting that 52/134 G3P[8] strains were equine-like.

Since 2006 G9P[4] have been detected at low numbers but at <1% of single strain infections. However, from 2015/16 numbers have been rising and in 2017/18 there were 279 detections and 284 in 2018/19 (7% and 5% of all single strain infections, respectively), in 2019/20 they maintained a similar prevalence of 6%, though absolute numbers fell (n=77). The majority of these were from the UK 369/640 (59%). Since the UK introduced rotavirus vaccination in 2013 there has been a relative increase in P[4] strains in the UK from 10% pre-vaccine introduction (5% in 2012/13) to 43% post-vaccine introduction (single typed strains only).

In 2018/19 there was an increase in the number of G8P[8] single strain detections (n=386), this compared to 15 detections in 2017/18. The majority of these were detected in samples from the UK (n=334). However, in 2019/20 G8P[8] was only detected in 19 samples across all counties. Rotavirus G8P[4] only became a significant emerging strain in the UK between 2008 and 2010, but to date has only been detected in a small number of cases in other European countries and was only detected in one sample in 2019/20 (Figure 6).

Vaccine status

In 2019/20 Italy, Spain, Greece and Finland reported data on vaccination status. In Italy vaccine status was known for 28% (n=26/94) of samples, 10/26 were vaccinated. For Spain vaccine status was recorded for only 9/81 individuals. In Finland only 12% (14/114) of samples had vaccination status recorded, of these 6/14 were vaccinated. For Greece 100% of samples had vaccine status included in epidemiological data, of these, none were reported as vaccinated. Drawing conclusions from these data is inadvisable because of the low number of samples with vaccination status recorded.

Figure 6. Distribution of genotypes G8P[8], G9P[4] and G8P[4] by rotavirus season and country, between September 2006 and August 2020.

Vaccine-derived strains

Currently only the UK, Austria, Spain, Finland and Germany report vaccine-derived strains to EuroRotaNet. The UK uses the Rotarix™ vaccine, with two doses provided at 2 months and 3 months of age respectively. In 2019/20 199/434 (46%) specimens were identified as G1P[8] Rotarix™ vaccine-derived strains in UK; of these 184 of the G1P[8] vaccine-derived strains were detected in children under 6 months of age, 11 in children 6-11 months of age and four in older children (two aged 12-23 months and two aged 2-4 years). Germany reported two, Spain one and Austria reported three G1P[8] vaccine-derived strains, these were all detected in children aged four months or younger. Austria, also reported three detections of RotaTeq™ derived strains in 2019/20, all in children 7 months or younger.

Children aged 2 to 6 months (in line with Rotarix™ vaccine schedule) are most likely to be shedding vaccine strain post-vaccination and gastroenteritis symptoms could be caused by other gastroenteritis causing pathogens or have symptoms that are associated with non-infectious aetiologies (35). Additionally, history of vaccination for the UK is not available in the EuroRotaNet database at present. The detection of G1P[8] vaccine-derived strains in older vaccine-eligible and vaccine-ineligible children and adults would potentially suggest some horizontal transmission from vaccinated infants or persistent shedding in a inadvertently vaccinated immunosuppressed child, such as those with severe combined immune deficiency.(36)

The relatively high proportion of rotavirus vaccine-derived strains detected in the UK may to some extent be the result of the introduction of sensitive molecular methods for rotavirus detection as part of syndromic diagnostic approaches in which samples are tested for the presence of multiple pathogens simultaneously, in several of the UK diagnostic laboratories. These methods can detect rotavirus shedding, and vaccine strain shedding at low viral loads with significantly higher sensitivity than antigen detection methods (such as ELISAs or near-patient type assay based on immunochromatography) (37). Because of this the WHO specify that RT-PCR is not recommended for the diagnosis of rotavirus disease (38). Detailed characterization through whole genome sequencing to monitor genetic drift and potential reassortment should inform the likelihood that vaccine strains are circulating more widely in the population or whether these findings are more likely to represent direct transmission from a recently vaccinated infant/vaccine-strain shedder. However, it is important to note that although vaccine-derived strains have been detected in stool samples it does not necessarily follow that any gastroenteritis symptoms are caused by the vaccine-derived strain.

Discussion

In the 2019/20 rotavirus season the number of typed rotavirus samples in the EuroRotaNet network declined substantially. This was indirectly due to the COVID-19 pandemic which began in Wuhan, China in December 2019 and hit Europe in early 2020, being declared a pandemic by the WHO on 11th March 2020. The low number of samples typed in 2019/20 mean that results must be interpreted with greater caution than previous years. Particularly, for countries that were not able to meet the WHO minimum threshold of 50-60 randomly selected rotavirus positive samples typed per country.

In 2019/20 the proportion of G1P[8] strains amongst the countries contributing samples remained low. Though G3P[8] was proportionally the most detected strain (22%), strain dominance varied by country. Of those countries typing significant numbers of specimens in 2019/20 France and Finland were the only countries were the majority of single type samples were of one genotype (G3P[8] and G9P[8]).

In the context of widespread vaccination across EuroRotaNet, it is important to monitor the possible vaccine-induced replacement of circulating genotypes or whether there is an emergence of genotype variants or antibodies escape mutants. In the United Kingdom G1P[8] was the predominant genotype causing rotavirus infections, prior to the introduction of vaccination in July 2013. Since then, the proportion and absolute number of infections caused by G1P[8] has declined with a shift to P[4] types, in particular G2P[4] and G9P[4] in 2018/19 and 2019/20.

Germany also introduced routine rotavirus vaccination in 2013 (both rotavirus vaccines are available) and has since seen a decline in the number of infections caused by genotype G1P[8]. Since vaccine introduction in Germany and the UK there has been a significantly reduced burden of rotavirus disease in young children (4,5,39,40). However, through data submitted to EuroRotaNet we cannot infer whether there is an increase in incidence of infections caused by P[4] types. Both vaccines are available in Germany but at present we do not have coverage data for Rotarix™ and RotaTeq™ by region, such data would be useful in interpreting any role of a given rotavirus vaccine on shifts in strain distribution.

However, countries which currently use or have previously used Rotarix™ for vaccination (Austria, Belgium, Germany and UK) had a mixture of either G2P[4] or G3P[8] dominating since vaccine introduction. Belgium has seen seasonal swings between G3P[8] and G2P[4] since 2007/08. Though, the increase in recent years of G3P[8] has been present across countries regadless of vaccine introduction status and levels of vaccine coverage.

Sweden, a country with regional rotavirus vaccination since 2014 has been experiencing reductions in the relative contribution of G1P[8] since 2011/12, and an increase in G3P[8]. Following the incorporation of rotavirus vaccination (with Rotarix™) into national paediatric immunisation schedule in September 2019 G1P[8] detections

have remained low.

Austria sees a sustained high level of G2P[4] strains detected which may be explained in part by the high proportion of rotavirus positive samples submitted to EuroRotaNet that came from adults and the elderly, accompanied by the reduction of peadiatric rotavirus cases (due to the rotavirus vaccination programe) who may have otherwise been predominantly infected with G1P[8] and/or other genotype constellation 1 (Wa-like) strains.

Despite the decrease in G1P[8] strains in all the countries under surveillance, the dominance of G2P[4] strains has previously only been detected in four of the five countries that have included Rotarix™ in their infant immunisation programmes. Whereas in Finland, the only country which exclusively uses RotaTeq™ there has been significant strain diversity and seasonal variation with no clear dominance of any one strain type. These finding should not be interpreted as strain replacement or vaccine failure, but in the context of a significantly reduced burden of disease in these countries (4,39–45). Unlike G2P[4], G3P[8] is included in genotype constellation 1 (Wa-like) and therefore the rise in G3P[8] is more likely to be attributed to natural temporal variation in genotype distribution, re-inforced by the evidence that relative increases of G3P[8] strains occurred in countries both with (Austria, Belgium, Germany, Finland Sweden and the UK) and without rotavirus vaccination in their national immunisation programme (e.g. France and Slovenia).

In the UK in 2019/20 a significant number of vaccine-derived rotavirus strains continued to be detected, mostly in young infants. Linking of the genotyping data to the vaccination records as well as the investigation of other aetiologies which cause gastroenteritis symptoms will be important in order to interpret this data more accurately.

Conclusion

In 2019/20 the COVID-19 pandemic impacted on rotavirus detections and therefore the number of rotavirus positive samples available and successfully typed. Therefore, 2019/20 findings for most EuroRotaNet countries should be interpreted cautiously. No novel emerging strains have been detected in any of the countries under surveillance during the rotavirus season 2019/20. There continues to be no evidence that rotavirus vaccination programs are driving the emergence of vaccine escape strains. In the context of significantly reduced rotavirus disease incidence in European countries with rotavirus vaccine programmes, there has been decline in proportion and absolute number of infections caused by G1P[8] in all the countries under surveillance. It appears that the consistent year on year decline in G1P[8] strains in countries with and without infant rotavirus immunisation schedules may suggest that the increase in vaccinated cohorts across Europe is having an impact across borders. Shifts in strain distribution and predominant type in the post-vaccine era need to be interpreted with care.

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APPENDICES

A.Table 1. Distribution of common rotavirus genotypes in 12 European countries in consecutive seasons between September 2006 and August 2020. (*Totals are total strains typed*).

Genotype	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*Total*
								Austria							
G2P4					130	82	78	164	14	28	130	21	66	14	727
G3P8					2	2	1	12	6	24	54	78	36	8	223
G1P8					22	21	17	8	28	18	21	4	23	1	163
G9P8					2	16	2	9	8	21	24	20	35	1	138
G4P8					6	12	3	5	6	9	1	3		1	46
G12P8							1		3	5	8	2	3	1	23
G9P4					5			1	1	4	2	2	5		20
Total					289	190	114	202	67	114	244	138	173	33	1564
								Belgium							
G2P4		245	189	215	84	112	244	26	79	54	363	104	17	25	1757
G3P8		23	61	7	162	48	57	77	139	27	36	115	245	11	1008
G9P8		81	47	13	41	65	22	87	167	173	59	55	105	6	921
G1P8		192	61	110	100	31	28	30	28	19	16	30	12	10	667
G4P8		55	36	16	115	4	19	8	76		3	5	1		338
G12P8		6		12	4	12		6	131	1		8	18	2	200
G9P4			1	1	6				2		2	5	59	25	101
Total		610	413	381	527	281	373	239	623	278	482	323	482	84	5096
								Denmark							
G1P8	84	182	122	162	104	35	30	95	62	14	17	25	4	1	937
G9P8	29	5	6	6	16	92	77	38	43	31	12	24	153	6	538
G3P8	7	7	9	9	42	47	8	5	44	25	131	23	50	2	409
G4P8	7	28	46	57	26	24	31	17	35	2	3	2			278
G2P4	28	3	31	27	5	5	21	23	9	5	7	8		1	173
G9P4			2	13	2				2	2		14	3		38
G12P8	6	1	1			2	1	5	1		2	4	3		26
Total	185	277	260	318	225	231	190	196	210	81	179	108	245	11	2716
								Finland							
G1P8	72	142	54	8	41	28	21	49	51	22	11	6	3	1	509
G9P8	41	31	14	4	2	9	9	13	35	29	38	58	42	51	376
G3P8	6	19	39		8	4	16	19	25	16	38	45	50	8	293
G4P8	3	60	85	29	35	7	8	35	11	3	3	4	2		285
G12P8	1		26			1	6	4	15	8	43	158	5	7	274
G2P4	15	9	5	5	4	2	13	55	61	21	21	18	31	10	270
G9P4				1		1		1		2	42	19	16	1	83
Total	142	266	227	52	98	58	77	187	203	112	209	331	188	114	2264
								France							
G1P8	273	513	460	581	668	468	758	634	621	175	86	127	52	19	5435
G9P8	121	179	194	87	66	127	74	280	410	656	685	382	350	41	3652
G3P8	13	17	35	16	37	164	170	170	19	62	33	171	233	134	1274
G2P4	53	15	48	157	37	51	50	18	79	39	64	43	21	16	691
G4P8	4	2	47	17	67	7	25	19	13	44	7	19		1	272
G12P8	2	7	1		2	36	35	8	23	23	4	33	19	52	245
G9P4				1	2	3	3	1	1	3			3		17

Genotype	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*Total*
Total	578	766	810	923	909	880	1196	1259	1225	1059	946	831	734	290	12406
								Germany							
G1P8	9	405	176	284	140	158	123	3	24	22	27	9	4	1	1385
G4P8	17	285	381	182	98	41	26	14	42	14	4	4	1		1109
G2P4	4	130	88	62	51	77	43	12	50	40	136	71	179	1	944
G9P8	8	51	63	148	68	156	40	5	18	42	79	16	38	5	737
G3P8	1	54	17	36	11	5	7	7	7	41	95	45	58	2	386
G12P8		18		1		17	21	2	2	7	46	1	3		118
G9P4			3	4					2		6		5	2	22
Total	40	964	752	736	368	463	269	43	148	198	424	151	318	14	4888
								Greece							
G4P8			229	215	23	246	55	256	198	110	155	90	13	1	1591
G1P8			66	82	278	50	90	31	33	121	61	52	24	29	917
G2P4			40	36	29	144	62	69	15	15	6	16	66	25	523
G9P8			10	5	1	18	3	16	6		1	6	43	10	119
G12P8				30	9	3	9	2	3	1		2	10	7	76
G3P8			4	6	12	24	1	3		6	1	3	8	3	71
G9P4			1					2					38	10	51
Total			380	384	366	507	229	420	270	287	230	176	232	104	3585
								Italy							
G1P8	151	584	283	709	753	757	550	444	279	114	79	95	72	14	4884
G9P8	67	255	140	223	85	31	144	280	192	157	204	41	12	4	1835
G4P8	52	104	59	121	74	168	107	125	259	105	16	3	6	1	1200
G12P8	1	2	4		2	7	21	44	9	273	263	151	145	34	956
G2P4	51	64	34	76	55	159	84	103	12	36	19	6	23	2	724
G3P8		52	24	45	15	40	98	20	3	9	53	24	41	22	446
G9P4		12	5	1							3	7	2	1	31
Total	346	1290	753	1379	1121	1305	1118	1142	819	737	781	406	381	94	11672
								Slovenia							
G1P8	173	467	294	139	41	153	120	156	411	46	76	7	28	3	2114
G2P4	61	25	6	36	197	179	155	193	24	184	25	8	13	1	1107
G4P8	58	80	139	226	190	58	45	110	35	28	10	1	10	1	991
G3P8	20		3		3	1	17	12	2	33	120	14	93	20	338
G9P8	6	32	11	18	8	85	37	25	46	8	28	4	22	4	334
G12P8	2				13	4	11	11	2						43
G9P4		1										8	1		10
Total	353	631	468	436	473	494	394	513	528	314	280	46	176	31	5137
								Spain							
G1P8	176	468	349	275	407	531	90	374	136	27	15	29	240	23	3140
G9P8	273	37	18	208	19	138	145	85	83	219	329	13	140	2	1709
G12P8		1		2	140	433	15	72	179	240	22	46	19	24	1193
G3P8	16	25	16		111	53	34	67	157	22	160	417	85	11	1174
G2P4	5	7	55	80	80	93	146	37	14	17	9	26	68	4	641
G4P8	2	2	41	20		66	4	76	4	4	2		1		222
G9P4	1						1			1	19	23	5		50
Total	544	662	537	616	824	1479	495	748	604	543	579	563	589	81	8864
								Sweden							
G1P8	23	450	54	75	68	58	42	57	39	50	42	48	4	6	1016
G3P8	2	21	13	7	11	18	13	43	29	66	75	72	69	16	455

Genotype	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*Total*
G9P8	5	54	15	5	8	22	28	32	43	32	26	31	24	11	336
G2P4	1	15	2	12	14	23	53	91	24	13	26	22	31	6	333
G4P8	1	32	18	7	8	26	19	17	45	12	43	10	2		240
G12P8				1	2	2	3	2	5	1	13		2	4	35
G9P4			1				3				2	10	4	3	23
Total	32	578	115	109	111	150	169	258	200	203	234	207	152	62	2580
	United Kingdom														
G1P8	523	626	437	647	419	419	417	233	158	43	19	33	38	14	4026
G2P4	119	65	106	26	51	24	47	29	354	339	1317	163	465	39	3144
G3P8	48	74	137	26	15	88	179	201	105	64	51	245	384	37	1654
G9P8	73	43	53	34	127	88	226	48	195	143	115	138	189	18	1490
Rotarix-VD								64	85	67	89	147	156	199	807
G4P8	12	49	94	47	18	133	68	56	105	24	4	4	65	2	681
G12P8	8	2	9		35	26	75	19	249	21	22	53	24	2	545
G9P4	3		4		1	1	1		13	14	27	191	143	35	433
Total	845	910	975	877	681	792	1075	673	1289	770	1763	1084	1959	434	14127

A.Table 2. Genotypes found in single rotavirus strain infections, between September 2006 and August 2020 (all countries)

Genotype	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*Total*
G1P8	1484	4029	2356	3072	3041	2709	2286	2114	1870	671	470	465	504	122	25193
G9P8	623	768	571	751	443	847	807	918	1246	1511	1600	788	1153	159	12185
G2P4	337	578	604	732	737	951	996	820	735	791	2123	506	980	144	11034
G3P8	113	292	358	152	429	494	601	636	536	395	847	1252	1352	274	7731
G4P8	156	697	1175	937	660	792	410	738	829	355	251	145	101	7	7253
G12P8	20	37	41	46	207	543	198	175	622	580	423	458	251	133	3734
G9P4	4	13	17	21	16	5	8	5	21	26	103	279	284	77	879
Rotarix-VD								64	85	67	89	148	160	205	818
G8P8	2	1	6		6		2	7	3	35	34	15	386	19	516
G2P8	22	32	20	9	12	32	39	14	10	4	39	12	28	2	275
G3P4	1	1	4	21	4	2	1	3	4	4	12	7	71	18	153
G8P4		1	59	78	5					3	1			1	148
G1P4	9	23	16	10	15	14	5	1	1		6	1	1	5	107
G12P6	1	4	11	7	8	2	7	2	1	3	11	13	6	12	88
G4P4	1	5	18	6	1	9	2	3	1	2			2		50
G8P14		1	2	3		3	1	1		7	4	1	8	14	45
G10P8		6	15	10	2	1		1	2		1		2	2	42
G6P14	1	2		8	1	5	1	4	2	2	3	3	3	6	41
G3P6			16	5			2	1	4	4	2	2	1	1	38
G2P6	5	16	2	6			2	2	1	1			1	1	37
G3P9			1	2	1	2		5	1	3	1	2	7	10	35
G12P4			3		2	3				3	1	6	4		22
G1P6			3	2	1		7	1		2	3	3			22
G6P8		2	1	1	3	3	2			1			3	5	21
G4P6	2		1	2	1			4	4	1	2	1	1	1	20
G9P6	1		1				1		4	2	2	1	2	2	16
G6P6				1	2	1	2	4			4		1		15
G3P14					1	1		2		1		1	2	4	12
G6P9	2	1	1	1		2	2	1		1					11
RotaTeq-VD											1	3	3	3	10
G4P9		1	5	1									1	2	10
G3P3						1			1	5	1			1	9
G10P14	5	1						1						1	8
G8P6	4	1	1	1											7
G9P9	1	1				2							1	1	6
G9P10		1	1										3	1	6
G1P5					2			1		1	1				5
G10P4	1	2											1		4
G2P9	1	1												1	3
G4P10			2					1							3

G1P8-UK-Unknown										3					3
G29P9												2			2
G6P5				1		1									2
G6P4		1								1					2
G2P10	1												1		2
G4P14				2											2
G6P11	1														1
G1P9								1							1
G12P10								1							1
G1P14					1										1
G10P5										1					1
G10P10		1													1
G2P1								1							1
G6P1														1	1
G10P9												1			1
G12P11													1		1
G12P9					1										1
G6P10										1					1
G9P11														1	1
Mixed or partially typed	267	435	379	323	390	405	317	348	203	209	316	249	304	116	4261
Total	3065	6954	5690	6211	5992	6830	5699	5880	6186	4696	6351	4364	5629	1352	74899