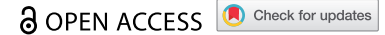


RESEARCH ARTICLE



Systematic literature review and meta-analysis on the prevalence of rotavirus genotypes in Europe and the Middle East in the post-licensure period

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ABSTRACT

Previous systematic literature reviews of rotavirus genotype circulation in Europe and the Middle East are limited because they do not include country-specific prevalence data. This study documents country-specific evidence on the prevalence of rotavirus genotypes in Europe and the Middle East to enable more precise epidemiological modeling and contribute to the evidence-base about circulating rotavirus genotypes in the post-vaccination era. This study systematically searched PubMed, Embase and Scopus for all empirical epidemiological studies that presented genotype-specific surveillance data for countries in Europe and the Middle East published between 2006 and 2021. The STROBE checklist was used to assess the quality of included studies. Proportional meta-analysis was conducted using the generic inverse variance method with arcsine transformation and generalized linear-mixed models to summarize genotype prevalence. Our analysis estimated the genotype prevalence by country across three date categories corresponding with rotavirus seasons: 2006–2010, 2011–2015, 2016–2021. A total of 7601 deduplicated papers were identified of which 88 studies were included in the final review. Rotavirus genotypes exhibited significant variability across regions and time periods, with G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and, to a lesser extent G12P[8], being the most prevalent genotypes through different regions and time-periods. Uncommon genotypes included G3P[9] in Poland, G2P[6] in Iraq, G4P[4] in Qatar, and G9P[4] as reported by the European Rotavirus Network. There was high genotype diversity with routinely identified genotypes being G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8]; there was high variability across time periods and regions. Continued surveillance at the national and regional levels is relevant to support further research and inform public health decision-making.

SUMMARY

This study synthesizes data from rotavirus surveillance studies to characterize genotype-specific prevalence of rotavirus in Europe and the Middle East following the licensure of rotavirus vaccines in 2006. In line with previous pan-European studies, results highlight the lack of a single dominant genotype across this time period. There was high genotype diversity with G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8] being the most commonly identified genotypes through different regions and time-periods.

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Rotavirus; vaccination; epidemiology; child health; diarrhoea

Background

Rotavirus infections are one of the world's leading causes of severe diarrhea and dehydration among children under five years of age.¹ Transmitted through an oral-fecal route, rotaviruses are highly contagious and estimated to infect nearly all children by the age of five.¹

Rotavirus contains a genome composed of 11 segments of double-stranded RNA that encode six structural proteins (VP1–VP4 and VP6–VP7) and six nonstructural proteins (NSP1–NSP6).^{2,3} Previous studies estimating the genotype-specific prevalence of rotavirus have mainly used glycoprotein (G) and protease-sensitive protein (P) type data.^{4–6} These

genotype classifications are largely based on two outer viral proteins: VP7 and VP4, respectively. G genotypes refer to the glycosylated VP7 protein on the virus's surface whereas P genotypes refer to the protease-sensitive VP4 spike protein on the virus's surface.⁵

Since 2006, two vaccines, Rotarix™ (RV1) and RotaTeq™ (RV5), have been available globally. Rotarix™, a monovalent vaccine developed by GSK Biologicals, Belgium, is derived from a single common genotype of human rotavirus and contains G1P[8]. A full course of Rotarix™ consists of two doses given orally, 4 weeks apart, between 6 and 24 weeks of age.⁷ RotaTeq™ is a pentavalent vaccine developed by Merck & Co., Inc., Kenilworth, NJ, USA, containing five human bovine

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reassortants G1, G2, G3, G4 and P[8].⁸ RotaTeq™ is administered orally and consists of three doses between the ages of 6 and 32 weeks.⁷

A systematic literature review performed in the early post-licensure period synthesized global longitudinal data from 2006 to 2010, and suggested that, in this period, genotype prevalence data did not show any consistent pattern indicative of selection pressure resulting from vaccine use and that six genotype combinations were mostly responsible for human rotavirus infections globally (G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] and G12P[8]).⁵ A more recent review showed a transient increase of G2P[4] following recent vaccine introduction.⁶ However, the latter did not present results by country.

Since the last country-specific systematic review in 2010,⁵ genotyping studies have been published. In this study, we synthesized available evidence using meta-analysis to provide an updated view of rotavirus genotype circulation in the post-licensure period (2006–2021) by country and region. This systematic literature review and meta-analysis provides the latest rotavirus genotype circulation by country in Europe and the Middle East to enable more precise epidemiological modeling and contribute to the evidence-base about circulating rotavirus genotypes in the post-vaccination era.

Methods

This systematic literature review was undertaken according to the principles of systematic reviews established in the Cochrane Handbook and guidance document published by the Center for Reviews and Dissemination (CRD) of York University, United Kingdom. We used the PRISMA checklist and guidelines for systematic reviews to report results.⁹

Data sources and searches

We systematically searched PubMed, Embase and Scopus for all empirical epidemiological studies presenting genotype-specific prevalence of rotavirus in countries and regions after rotavirus vaccine licensure in 2006 (search strategies in Appendix I). We also searched Google and Google Scholar to identify gray literature, such as surveillance reports.

The population of interest encompassed all people living in Europe and the Middle East (Table 1). The primary outcome

was the prevalence of circulating genotypes after the licensure of rotavirus vaccines. Secondary outcomes included the prevalence of genotypes by region. Studies were eligible for inclusion if they were empirical epidemiological studies, including longitudinal studies, and cross-sectional studies from multiple time points within the same setting. We included all studies meeting these inclusion criteria and that were published between January 2006 and up to 25 August 2021. Records in languages other than English were eligible for inclusion and were translated using Google Translate.¹⁰

Studies were excluded if their study design deviated from empirical epidemiological research, or they did not provide surveillance data on observed genotype circulation. Additionally, we excluded editorials, published abstracts, conference proceedings, and studies that were inaccessible. For feasibility, and to select the most representative studies, we excluded studies lacking at least six consecutive months of surveillance. To maximize the number of studies included while maintaining an acceptable statistical sample,¹¹ we excluded studies with fewer than 30 rotavirus positive samples. Studies published before 2006 or studies that did not contain extractable post-2006 data were also excluded.

Study selection

An initial screening of titles and abstracts was performed by one reviewer to eliminate studies that did not mention rotavirus genotype prevalence. To minimize bias, two reviewers subsequently evaluated the titles and abstracts of all studies in accordance with the established inclusion and exclusion criteria. Any titles and abstracts that did not clearly meet our exclusion criteria were considered for a full-text review, which was carried out independently by two reviewers. Any discrepancies were resolved through discussion between the two reviewers.

Data extraction

A data extraction form was created to collate relevant data, including circulating genotypes and age distribution data. The form was tested by two researchers on one study to confirm that it effectively captured the relevant data. Subsequently, one reviewer conducted the data extraction, and a second reviewer

Table 1. Inclusion and exclusion criteria.

PICOTS	Descriptions
Inclusion criteria	
Population(s)	All populations in Europe and the Middle East
Interventions	All rotavirus vaccines
Comparators	Not applicable
Outcomes	<ul style="list-style-type: none"> • Primary outcome: prevalence of rotavirus genotypes after vaccine introduction • Secondary outcome: genotype dominance by geographic region (i.e. continent or country after vaccination)
Timing	All studies with data collection period between 2006 and August 2021
Study design	Empirical epidemiological studies (sample serology testing)
Exclusion criteria	
Any study with the following characteristic	<ul style="list-style-type: none"> • Studies published before 2006 or that did not contain extractable post-2006 data • Less than 30 positive rotavirus samples • Countries not in Europe and the Middle East • Studies lacking at least six consecutive months of surveillance or studies with two cross-sections fewer than not 6 months apart

independently cross-checked the extracted data. Any discrepancies were resolved through discussion.

Quality assessment of included studies

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to assess the quality of the observational studies included.¹² All studies that met the inclusion criteria were reviewed with the STROBE checklist for quality appraisal by one reviewer. Each completed STROBE checklist was further reviewed by a second independent reviewer.

Analyses

We examined rotavirus prevalence in five regions. European regions were categorized as Western Europe, Eastern Europe, Northern Europe, Southern Europe, as defined by the United Nations Statistical Division.¹³ Countries belonging to the Middle East were defined as per the United Nations World Tourism Organization¹⁴ (see Appendix II). To facilitate the comparison of data while maintaining a level of granularity, we summarized the genotype-specific prevalence of rotavirus both at the country and regional levels across three time spans: 2006–2010, 2011–2015, 2016–2021. For studies with two overlapping time periods, we categorized the studies based on rotavirus seasons. For example, Spring 2006–Summer 2010; Autumn 2010–Winter 2015; Spring 2015–25 August 2021.

For each available combination of country (or region), time period, and rotavirus genotype, we conducted meta-analyses to estimate overall prevalence of the genotype. If there was only one prevalence record available, we calculated the overall prevalence based on that single record. For each study, we required information on the total number of samples tested and the number of samples positive for each genotype. The individual yearly estimates of genotype prevalence were incorporated into the meta-analysis. In cases where a study lacked year- or season-specific data and had data overlapping with predefined periods, we assigned the study to the period with the most overlapping years of data collection. To avoid double counting, because investigators may submit national results to regional networks and both may be summarized independently, we assessed multi-country pan-European studies and reports using a narrative synthesis and did not include the data in our meta-analysis. Additionally, studies that reported only G or P types were reported narratively and not included in our meta-analysis.

We conducted proportional meta-analysis using random effects models because we assumed that within each country, region, and time-period the true underlying prevalence will differ between studies conducted in different populations and settings.¹⁵ To conduct the meta-analysis, we applied the arcsine transformation to each proportion (p) ($\arcsin(\sqrt{p})$), used the generic inverse variance method to pool the transformed proportions and back-transformed the pooled estimate to the original scale.¹⁶ We estimated the between-study variance using the restricted maximum-likelihood estimator,¹⁷ and calculated the 95% confidence intervals for the random effects estimate using the DerSimonian and Laird method.¹⁸ To assess

the sensitivity of our method, we also conducted a meta-analysis using generalized linear-mixed models,¹⁶ estimating the between-study variance using the maximum-likelihood estimator and again calculating the 95% confidence intervals for the random effects estimate using the DerSimonian and Laird method.^{15,17,18} Heterogeneity was evaluated using the I-squared (I^2) statistic. We interpreted the I^2 statistics following guidelines in the Cochrane Handbook with 0%–40%, 30%–60%, 50%–90% and 75%–100% suggesting unimportant, moderate, substantial and considerable heterogeneity respectively.⁹ All analyses were conducted using R version 4.2.3¹⁹ and the meta package version 6.5-0.²⁰

Results

Search results

The search of electronic databases identified 7,601 deduplicated papers (Figure 1). We excluded 7,479 studies during title and abstract screening because they did not include data in the country or region of interest or were not empirical epidemiological studies reporting observed genotype circulation data. In total, 122 records appeared to meet the inclusion criteria during title and abstract screening of which 119 papers were able to be retrieved to proceed with full text screening. Three studies could not be retrieved through a review of databases and online search engines and were subsequently excluded. Other records were excluded following full text screening because: 1) small sample size (<30) ($n = 8$); 2) not empirical epidemiological studies reporting observed genotype circulation data ($n = 8$); 3) contained data that could not be extracted post 2006 ($n = 7$); 4) not a full paper ($n = 3$); 5) wrong setting ($n = 3$); 6) wrong study design ($n = 2$); 7) less than six months consecutive data ($n = 1$). In total, eighty-seven empirical epidemiological studies met the inclusion criteria and were included in the review in addition to one report identified as gray literature (see Appendix III for a visual representation on data availability). For ease of readability, we present meta-analysis results using the generic inverse variance method with arcsine transformation. Results of this method were largely consistent with meta-analysis results using the generalized linear-mixed models, which are available upon request.

Eastern Europe

For the period 2006–2010, genotype prevalence data were available from 3,114 positive rotavirus samples, taken from 20 records from eight studies, across seven countries (Figure 2a).^{21–28} Based on within-country meta-analyses, the most common rotavirus genotypes in the region were G4P[8] and G1P[8], representing 30% (95% CI: 17%, 45%) and 27% (95% CI: 17%, 38%) of circulating genotypes, respectively.

G4P[8] was the most prevalent genotype in Belarus and Hungary, representing 58% (95% CI: 48%, 68%) and 33% (95% CI: 29%, 38%) of genotypes, respectively. In both countries G1P[8] was the second most common genotype, with a prevalence of 14% (95% CI: 8%, 21%) in Belarus and 30% (95% CI: 26%, 34%) in Hungary. G1P[8] was the most common genotype in the Russian Federation with 42%

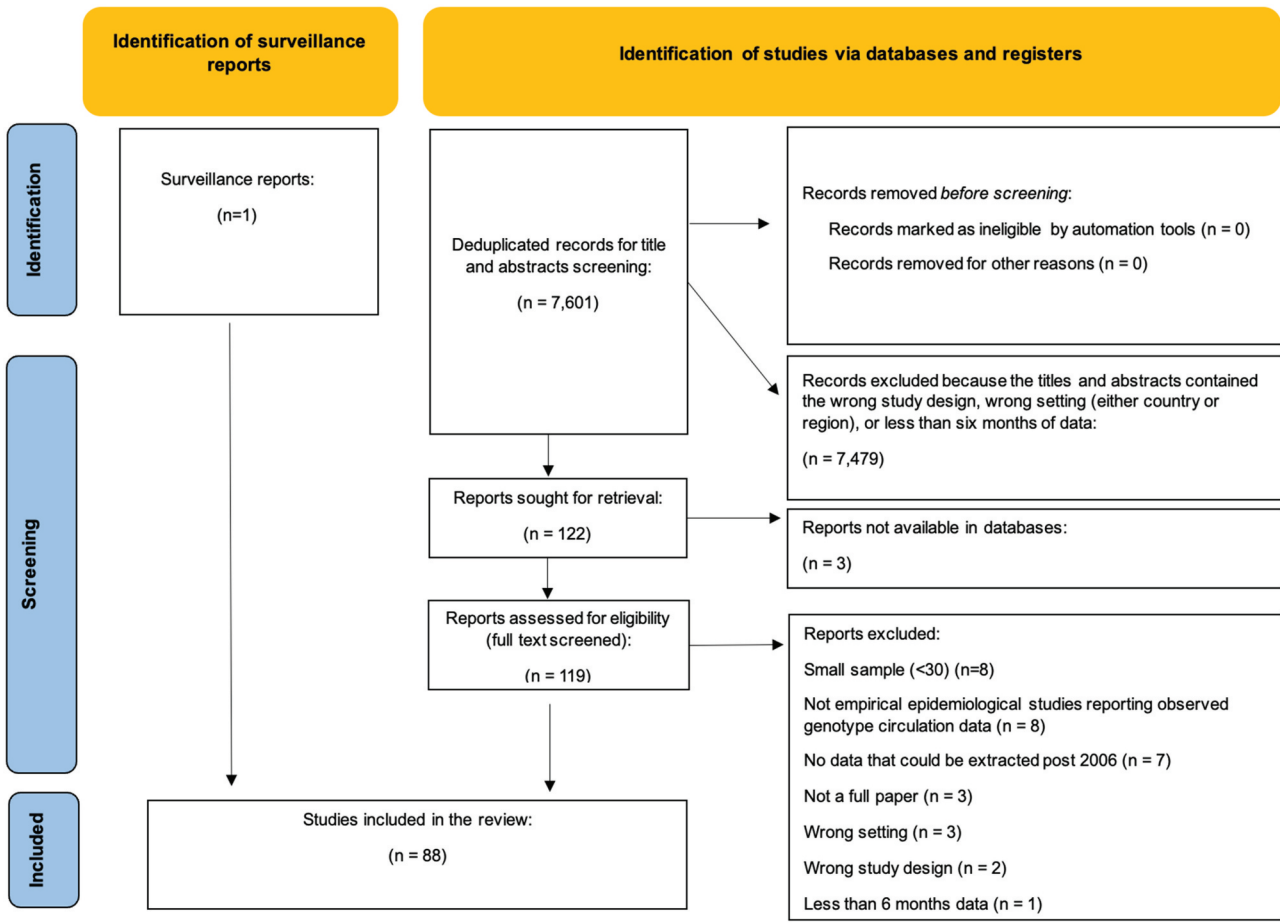


Figure 1. PRISMA flow diagram.

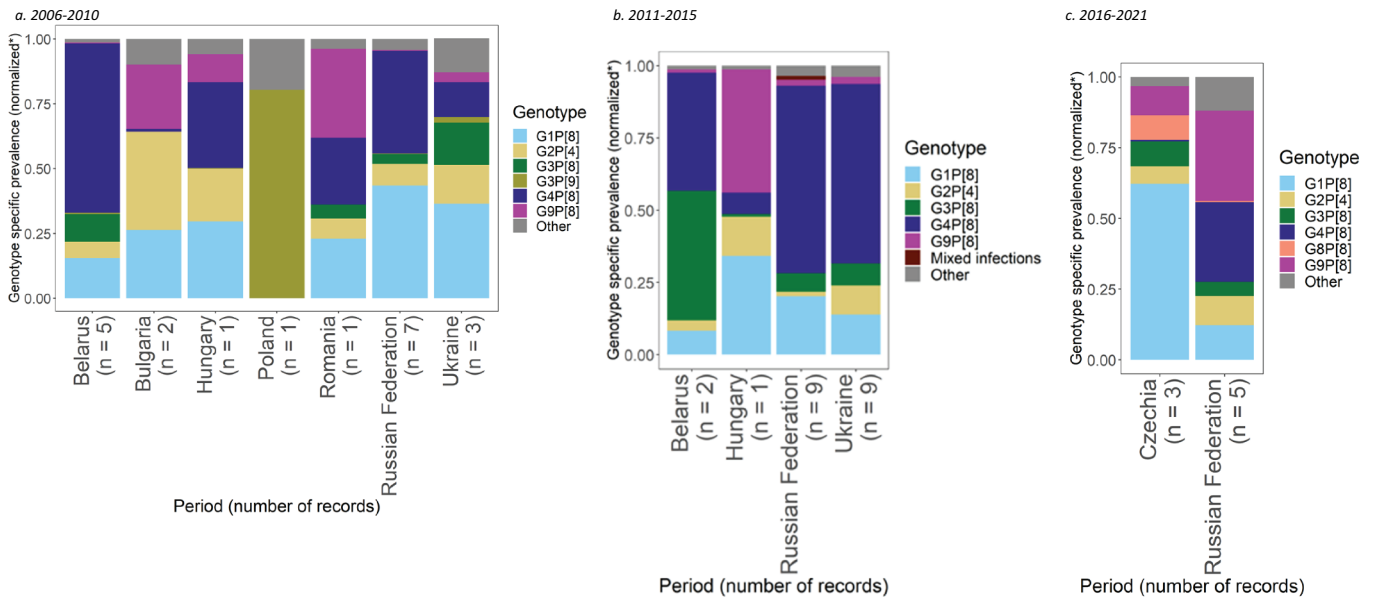


Figure 2. Prevalence of the most common rotavirus genotypes in Eastern Europe.

(95% CI: 20%, 65%), followed by G4P[8] with 38% (95% CI: 15%, 65%). G1P[8] was also the most dominant in Ukraine with 37% (95% CI: 20%, 56%), followed by G3P[8] with 17% (95% CI: 0%, 50%). G2P[4] was the most prevalent genotype in Bulgaria 36% (95% CI: 18%, 57%), followed by

G1P[8] with 25% (95% CI: 3%, 59%). In Poland, G3P[9] was the predominant genotype at 80% (95% CI: 67%, 90%). G9P[8] was most common in Romania with 34% (95% CI: 30%, 39%), followed by G4P[8] with 26% (95% CI: 22%, 30%).

For the period 2011–2015, genotype prevalence data were available from 2,887 positive rotavirus samples available from 21 records from eight studies, across four countries (Figure 2b).^{21,22,25,26,29–32} Based on this data, the most common rotavirus genotype in the region was G4P[8], representing 56% of circulating genotypes (95% CI: 46%, 66%), followed by G1P[8], with 16% prevalence (95% CI: 11%, 23%).

G4P[8] was the most prevalent genotype in the Russian Federation and Ukraine with 63% (95% CI: 50%, 76%) and 59% (95% CI: 47%, 70%) prevalence, respectively. G1P[8] was the second most common genotype in both countries, representing 20% (95% CI: 9%, 33%) of genotypes in the Russian Federation and 13% (95% CI: 7%, 21%) in Ukraine. In Belarus, G3P[8] was the most prevalent genotype with 43% (95% CI: 7%, 85%), followed by G4P[8] with 39% (95% CI: 12%, 71%). In Hungary G9P[8] was the most dominant genotype with 43% (95% CI: 38%, 48%), followed by G1P[8] with 34% (95% CI: 30%, 39%).

Lastly, for the period 2016–2021, genotype prevalence data were available from two countries, representing 3,663 positive rotavirus samples available from 8 records from six studies (Figure 2c).^{30,33–37} Based on this data, the most common rotavirus genotypes in the region were G1P[8] and G9P[8], showing similar regional prevalences of 25% (95% CI: 10%, 44%) and 21% (95% CI: 9%, 37%), respectively. G1P[8] was the most dominant genotype in Czechia with 57% (95% CI: 38%, 75%), followed by G9P[8] with 10% (95% CI: 2%, 21%). G9P[8] was the most dominant genotype in the Russian Federation with 30% (95% CI: 13%, 51%), followed by G4P[8] with 27% prevalence, respectively (95% CI: 11%, 46%).

The Russian Federation was the only country included in meta-analyses across all three time periods. During these periods the dominant genotype varied. In 2006–2010, it was G1P[8] and G4P[8] with 42% and 38% prevalence, respectively. From 2011–2015, G4P[8] emerged as the dominant genotype with 63% prevalence, followed by G1P[8] with 20%. While from 2016–2021, G9P[8] emerged as the most prevalent genotype with 30% prevalence, followed by G4P[8] with 27%.

Northern Europe

For the period 2006–2010, genotype prevalence data were available from 1,525 positive rotavirus samples, taken from

11 records from six studies, across four countries (Figure 3a).^{38–43} Based on this data, the most common rotavirus genotypes in the region were G1P[8] and G2P[4], representing 49% (95% CI: 30%, 69%) and 13% (95% CI: 3%, 28%) of genotypes, respectively.

G1P[8] had the highest prevalence in three countries, with 58% prevalence (95% CI: 24%, 89%) in Finland, 68% (95% CI: 51%, 82%) in Ireland and 49% (95% CI: 3%, 97%) in Sweden. G2P[4] was the second most common genotype in Sweden with a prevalence of 23% (95% CI: 0%, 84%). In Estonia, G2P[4] was the most common genotype with a prevalence of 43% (95% CI: 1%, 94%), followed by G4P[8] with 19% (95% CI: 0%, 68%).

For the period 2011–2015, genotype prevalence data were available from 4,232 positive rotavirus samples, taken from 15 records from eight studies, across eight countries (Figure 3b).^{39,44–50} Based on this data, the most common rotavirus genotypes across all eight countries were G2P[4] and G1P[8], with a pooled prevalence across all analyzed samples of 25% (95% CI: 14%, 38%) and 23% (95% CI: 15%, 31%), respectively.

G1P[8] was the most prevalent genotype in Denmark and Finland, with prevalences of 42% (95% CI: 39%, 46%) and 30% (95% CI: 24%, 35%), respectively. In Denmark, the second most common genotypes were G4P[8] and G9P[8], each with a prevalence of 17% (95% CI: 15%, 20%). In Finland, G2P[4] was the second most common genotype with a prevalence of 22% (95% CI: 17%, 26%). G4P[8] was the most prevalent genotype with a prevalence of 44% (95% CI: 39%, 50%) in Estonia, 43% (95% CI: 27%, 61%) in Ireland, and 60% (95% CI: 56%, 65%) in Latvia. The second most prevalent genotype in both Estonia and Ireland was G1P[8] with prevalences of 30% (95% CI: 25%, 35%) and 35% (95% CI: 20%, 53%), respectively. In the United Kingdom of Great Britain and Northern Ireland, G1P[8] and G2P[4] were the most prevalent genotype with 20% (95% CI: 8%, 35%) and 16% (95% CI: 4%, 34%) prevalence, respectively. In Sweden, G2P[4] was the most prevalent genotype with a prevalence of 56% (95% CI: 34%, 77%).

From 2016 to 2021, genotype prevalence data were available from 1,810 positive rotavirus samples, taken from 15 records from eight studies, across five countries (Figure 3c).^{39,44–46,48,51–53} Based on this data, the most common rotavirus genotypes in the region were G2P[4] and G1P[8]

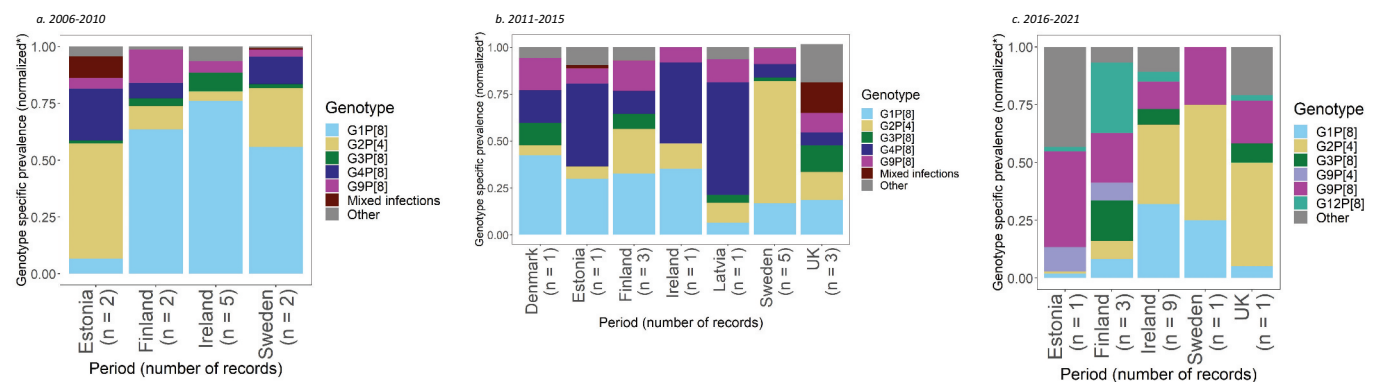


Figure 3. Prevalence of the most common rotavirus genotypes in Northern Europe.

[8], with a prevalence of 23% (95% CI: 12%, 35%) and 18% (95% CI: 8%, 30%), respectively.

G2P[4] was the most common genotype in Ireland, the United Kingdom of Great Britain and Northern Ireland and Sweden, with prevalences of 29% (95% CI: 15%, 46%), 45% (95% CI: 41%, 48%) and 56% (95% CI: 34%, 77%), respectively. In Ireland and Sweden, the second most common genotype was G1P[8] with a prevalence of 27% (95% CI: 12%, 46%) and 14% (95% CI: 2%, 36%), respectively. In the United Kingdom of Great Britain and Northern Ireland the second most common genotype was G9P[8] with a prevalence of 18% (95% CI: 16%, 21%). In Estonia, G9P[8] was the most common genotype with 41% (95% CI: 32%, 51%). In Finland, G12P[8] was the most prevalent genotype with 28% (95% CI: 7%, 55%), followed by G9P[8] with a prevalence of 20% (95% CI: 15%, 25%).

Three countries, Estonia, Ireland and Finland, were included in meta-analyses across all three time periods. In Estonia, G2P[4] was the dominant genotype from 2006 to 2010 with 43% prevalence, followed by G4P[8] with 19% prevalence. From 2011–2015, G4P[8] emerged as the dominant genotype at 44% prevalence followed by G1P[8] with 30% prevalence. Between 2016–2021, G9P[8] was the most common genotype, with 41%, followed by G4P[4] with 12% prevalence. In Finland, G1P[8] was the most prevalent genotype from 2006 to 2010 at 58% prevalence. Although remaining the most prevalent, the dominance of G1P[8] decreased during 2011–2015 to 30%, while and G2P[4] increased to 22% as the second most prevalent genotype. During 2016–2021, G12P[8] was the most observed genotype at 28%, followed by G9P[8] at 20%. In Ireland, G1P[8] was the most prevalent genotype from 2006 to 2010, with a prevalence of 68%. From 2011 to 2015, G1P[8] dropped to second most prevalent at 35%, behind G4P[8] with a 43% prevalence. From 2016–2021, G2P[4] led with a 29% prevalence.

Southern Europe

For the period 2006–2010, genotype prevalence data were available from 5,628 positive rotavirus samples, taken from 26 records from 14 studies, across five countries (Figure 4a).^{54–67}

Based on this data, the most common rotavirus genotypes in the region were G1P[8] and G9P[8], showing 42% (95% CI: 33%, 52%) and 14% (95% CI: 7%, 23%) prevalence.

In Albania, G1P[8] and G4P[8] were the most prevalent genotypes with 37% (95% CI: 31%, 44%) and 37% (95% CI: 25%, 51%) prevalence, respectively. G1P[8] was also the most prevalent genotype in Italy and Slovenia with 47% (95% CI: 39%, 56%) and 66% (95% CI: 46%, 84%) prevalence. In Greece, G4P[8] was the most prevalent genotype with 49% prevalence (95% CI: 10%, 88%), followed by G1P[8] with 22% (95% CI: 4%, 50%). While in Spain, G9P[8] was the most prevalent genotype with 44% (95% CI: 15%, 75%) prevalence, followed by G1P[8] with 38% (95% CI: 14%, 65%).

For the period 2011–2015, genotype prevalence data were available from 4,929 positive rotavirus samples, taken from 16 records from nine studies, across four countries (Figure 4b).^{56,60,64,68–73} Based on this data, the most common rotavirus genotypes in the region were G1P[8] and G4P[8], with prevalences of 42% (95% CI: 30%, 55%) and 12% (95% CI: 5%, 21%), respectively.

In Croatia and Italy, G1P[8] was the most common genotype with a prevalence of 63% (95% CI: 59%, 66%) and 46% (95% CI: 31%, 61%), respectively. The second most common genotype was G2P[4] in Croatia with 20% prevalence (95% CI: 17%, 23%) and G4P[8] in Italy with 13% (95% CI: 6%, 21%). In Greece, G4P[8] was the most prevalent genotype with 59% (95% CI: 50%, 67%), followed by G1P[8] with 14% (95% CI: 9%, 22%). In Spain, G12P[8] was the most common genotype with a prevalence of 36% (95% CI: 2%, 83%), followed by G1P[8] with 26% (95% CI: 17%, 35%) prevalence.

Italy was the only country in Southern Europe with data for the period 2016–2021. Genotype prevalence data were available from 2,429 positive rotavirus samples, taken from five records from three studies^{64,74,75} (4C). During this period, G1P[8] was the most prevalent genotype with 29% (95% CI: 19%, 40%), followed by G12P[8] with 27% (95% CI: 15%, 41%) prevalence.

Italy was the only country in Southern Europe to be included in the meta-analyses for all three time periods. Through the different time-periods, G1P[8] became less dominant, with the relative proportion of this genotype declining from 47% during 2006–2010, to 46% in 2011–2015, and 29% in

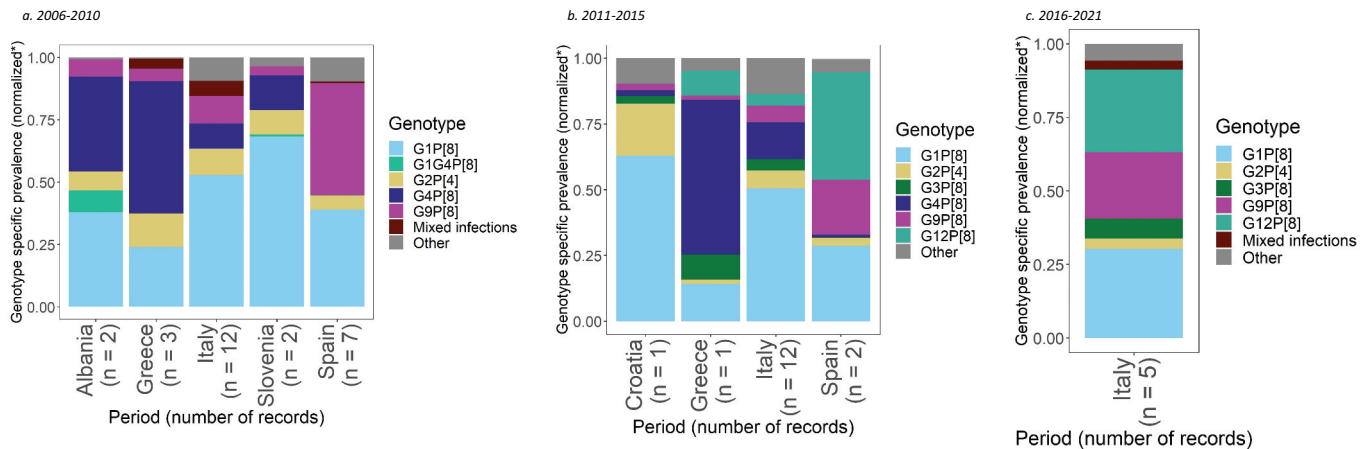


Figure 4. Prevalence of the most common rotavirus genotypes in Southern Europe.

2016–2021. The second most prevalent genotype varied from G9P[8] in 2006–2010, to G4P[8] from 2011–2015, and G12P[8] with a prevalence of 27%, from 2016–2021.

Western Europe

For the period 2006–2010, genotype prevalence data were available from 3,561 positive rotavirus samples from 12 records from seven studies, across four countries (Figure 5a).^{76–82} Across all rotavirus samples retrieved for this region, the most common rotavirus genotypes were G1P[8] and G2P[4], with a prevalence of 39% (95% CI: 27%, 53%) and 16% (95% CI: 7%, 28%), respectively. G2P[4] was the most prevalent genotype observed in Austria with 43% (95% CI: 24%, 64%) prevalence and Belgium with 43% (95% CI: 34%, 54%) prevalence. G1P[8] was the second most prevalent genotype in both countries with 26% (95% CI: 11%, 46%) prevalence in Austria, and 27% (95% CI: 13%, 45%) in Belgium. G1P[8] was most dominant in France with 59% prevalence (95% CI: 54%, 64%), followed by G9P[8] with 21% (95% CI: 15%, 28%). In Germany, G3P[8] was the most common genotype with a prevalence of 24% (95% CI: 0%, 100%), followed by G1P[8] with 19% (95% CI: 0%, 64%).

For 2011–2015, genotype prevalence data were available from 4,989 positive rotavirus samples from six records from three studies, across two countries, Austria and France (Figure 5b).^{78,82,83} Based on within-country meta-analyses or individual prevalence records, the most common rotavirus genotypes were G1P[8] and G9P[8], showing a prevalence of 57% (95% CI: 44%, 68%) and 14% (95% CI: 6%, 23%), respectively. In France, G1P[8] had a prevalence of 61% (95% CI: 53%, 69%), followed by G9P[8] with 15% (95% CI: 7%, 26%). G2P[4] was the most prevalent genotype in Austria with a prevalence of 68% (95% CI: 43%, 87%), followed by G1P[8] with 21% (95% CI: 6%, 46%).

For the period 2016–2021, genotype prevalence data were available from 1,202 positive rotavirus samples in two records from one study in France (Figure 5c).⁸³ Based on this data, the

dominant rotavirus genotype was G9P[8] with 72% (95% CI: 59%, 84%) prevalence. G1P[8] was the second most common genotype at only 12% (95% CI: 3%, 24%) prevalence.

One country, France, was included in meta-analyses across all three time periods. G1P[8] was the dominant genotype from 2006 to 2010, representing 59% (95% CI: 54%, 64%) of genotypes and 61% (95% CI: 53%, 69%) from 2011 to 2015. However, from 2016 to 2021, G9P[8] emerged as the dominant genotype with a prevalence of 72% (95% CI: 59%, 84%), with G1P[8] genotype prevalence decreasing to 12%.

Middle East

For the period 2006–2010, genotype prevalence data were available from 957 positive rotavirus samples, taken from seven records from seven studies, across seven countries (Figure 6a).^{84–90} Across these samples, the most common rotavirus genotypes reported were G1P[8] and G2P[4], with prevalences of 35% (95% CI: 14%, 59%) and 14% (95% CI: 2%, 36%), respectively.

G1P[8] was the most prevalent genotype in three countries: Jordan, Saudi Arabia and United Arab Emirates, representing 82% (95% CI: 76%, 87%), 59% (95% CI: 49%, 68%), and 59% (95% CI: 52%, 65%) of genotypes, respectively. G2P[4] was the most prevalent genotype in Oman and Yemen, with prevalences of 56% (95% CI: 47%, 66%) and 59% (95% CI: 46%, 71%). In Iraq, G2P[6] was the most prevalent genotype with 43% (95% CI: 31%, 55%) prevalence. In Lebanon, G4P[8] was the most prevalent genotype with a prevalence of 36% (95% CI: 28%, 45%), followed by G1P[8] with a prevalence of 27% (95% CI: 20%, 35%).

For the period 2011–2015, genotype prevalence data were available from 687 positive rotavirus samples, taken from five records from five studies, across four countries (Figure 6b).^{90–94} For these samples, the most common rotavirus genotypes were G1P[8] and G9P[8], showing prevalences of 36% (95% CI: 22%, 51%) and 20% (95% CI: 14%, 28%).

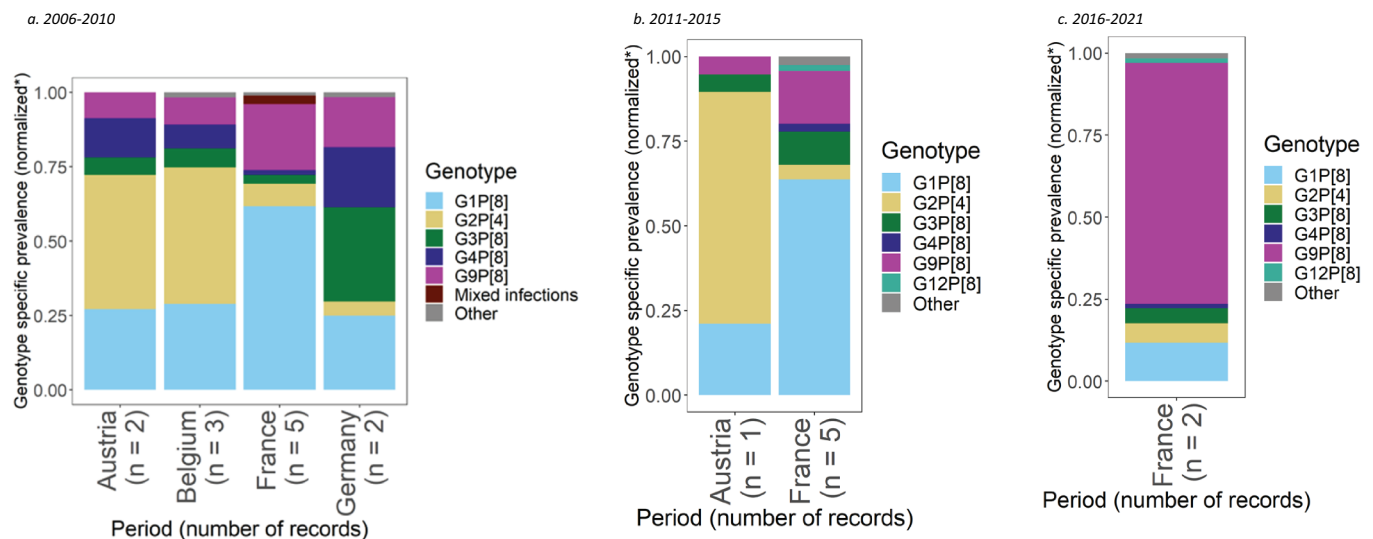


Figure 5. Prevalence of the most common rotavirus genotypes in Western Europe.

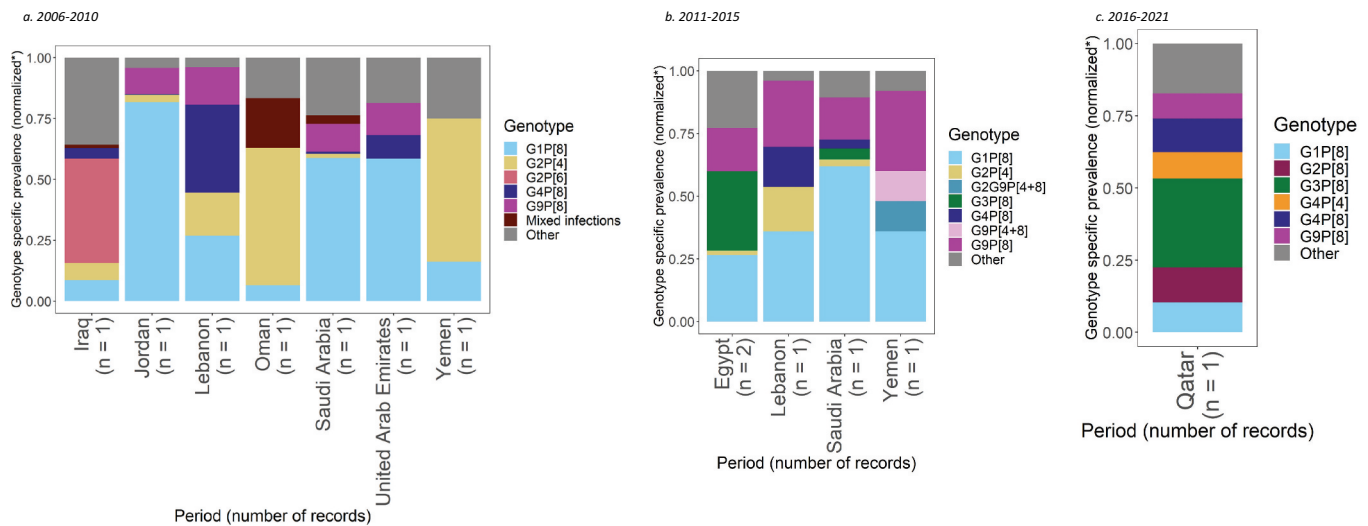


Figure 6. Prevalence of the most common rotavirus genotypes in the Middle East.

G1P[8] and G9P[8] were the most prevalent genotypes in Lebanon, Saudi Arabia and Yemen. G1P[8] and G9P[8] prevalence was 36% (95% CI: 31%, 41%) and 26% (95% CI: 22%, 31%) in Lebanon, 62% (95% CI: 52%, 71%) and 17% (95% CI: 10%, 25%) in Saudi Arabia, and 36% (95% CI: 18%, 57%) and 32% (95% CI: 15%, 54%) in Yemen, respectively. In Egypt, G3P[8] was the most prevalent genotype with a prevalence of 26% (95% CI: 8%, 50%), followed by G1P[8] at 22% (95% CI: 15%, 30%).

Qatar was the only country which included data for the period 2016–2021. Genotype prevalence data were available from 231 positive rotavirus samples, taken from one record in one study.⁹⁵ In Qatar, G3P[8] was the most prevalent genotype with a prevalence of 31% (95% CI: 25%, 37%). G2P[8] and G4P[8] were the second most prevalent genotypes, each representing 12% (95% CI: 8%, 17%).

Studies excluded from meta-analysis

Twelve studies were excluded from the meta-analysis because they: 1) reported only G or P types separately;^{96–102} 2) did not report the number of samples;¹⁰³ 3) were pan-European studies;^{104–106} and 4) included data from gray literature.¹⁰⁷

Among seven studies that reported only G types, G1 was the most identified type in three European settings from 2006–2010, including Denmark, Norway and Spain with reported prevalences of 39%, 55%, and 50%, respectively.^{96,97,99} G12 was most commonly identified in one study in Spain, representing 30% of genotypes reported from 2010 to 2018⁹⁸ and G4 was most commonly identified in one study in Greece with a prevalence of 60% from 2008 to 2010.¹⁰⁰ Two studies reporting G and P types separately also showed P[8] as the predominant P type, with prevalences of 85% and 75% from 2006 to 2010, respectively.^{97,100} In the Middle East, G1 was the most commonly identified genotype in two studies in Egypt, with prevalence varying from 44% from 2008 to 2010 to 55%.^{101,102} One study, which was excluded from the meta-analysis for not reporting the number of samples reported that G1P[8], G2P

[4], G4P[8] and G9P[8] represented 84–96% of genotypes from 2005 to 2013.¹⁰³

Three pan-European peer-reviewed studies in addition to the 2019 EuroRotaNet annual report were included for narrative synthesis. The EuroRotaNet surveillance network was established in 2007 and monitors rotavirus genotype diversity and year-to-year to identify genotype fluctuations across Europe. Two of the manuscripts summarized early results from member countries of EuroRotaNet,^{104,105} the third manuscript examined data from Czechia, Germany, Italy, Poland, Spain and the United Kingdom.¹⁰⁶ In the two studies investigating data from EuroRotaNet member countries, G1P[8] was the most prevalent aggregated genotype in every year from 2006 to 2009. Iturriza-Gómara 2009 showed G1P[8] accounted for 43% of genotypes from 2005 to 2006, 42% from 2006 to 2007, and 62% from 2007 to 2008.¹⁰⁴ Iturriza-Gómara 2010 showed G1P[8] accounted for 43% of genotypes from 2006 to 2007, 53% from 2007 to 2008, and 46% from 2008 to 2009.¹⁰⁵ The third study, using data from European countries from 2005–2007, showed that genotype distribution varied between countries.¹⁰⁶ G9P[8] was the most common type in Poland and Spain, G1P[8] was predominant in Czechia and Italy, and G4P[8] and G1P[8] were both prevalent in Germany. The 2019 EuroRotaNet annual report summarized information from all previous seasons and showed that G1P[8] was the most common identified genotype until 2015/2016.¹⁰⁷ In 2018/2019, G1P[8] was identified in 9% of samples, and G3P[8], G9P[8] and G2P[4] were detected in 19%–25% of samples. Seven genotypes circulated with a prevalence > 1%, including G1P[8], G4P[8], G2P[4], G9P[8], G3P[8], G12P[8], and G9P[4]. The report also shows that dominance of a single genotype has become rarer in recent years, while the relative proportion of less common genotypes has increased.¹⁰⁷

Discussion

We performed a meta-analysis of rotavirus genotypes circulating in Europe and the Middle East between 2006 and 2021,

providing an update to previously published systematic reviews and providing data for countries not included in EuroRotaNet. Our results highlight the lack of a single dominant genotype across time period, with G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8] frequently identified as the most prevalent genotypes. Because our results summarized individual country results, they can be used to characterize genotype circulation by country and are complementary to EuroRotaNet data.

Results from our meta-analysis are consistent with surveillance reports and pan-European studies,^{104–107} which characterize emerging genotype diversity across time in the post-licensure period and the decrease in prevalence of G1P[8]. According to EuroRotaNet annual report, G1P[8] genotype was consistently the most prevalent genotype between 2006–2007 and 2014–2015, ranging from a maximum of 62% in 2007–2008 to 31% in 2014–2015.¹⁰⁷ From 2015–2016, G9P[8] was found in 34% of single genotype infections characterized. In subsequent years, dominant genotypes also included G3P[8] and G2P[4].¹⁰⁷

Our study included two EuroRotaNet member countries that had data across all three time periods: France and Finland. Consistent with EuroRotaNet data, our analysis shows G1P[8] was the most prevalent genotype in France from 2006–2015, whereas from 2016 to 2021, G9P[8] emerged as the most prevalent genotype. Similarly, in Finland a decrease of G1P[8] was observed from 2011 to 2021, as the prevalence of G2P[4], G9P[8], and G12P[8] increased. Lastly, our results for the Middle East are consistent with a recent review in the Middle East and North Africa, which showed that G1P[8], G9P[8], and G2P[4] were the most common genotypes from 1980 to 2019.¹⁰⁸ Of note, our analysis shows G3P[8] as the most prevalent genotype from 2016 to 2021 in Qatar.

While we have not captured vaccination data in our review, we find that the prevalent genotypes remain consistent through 2006–2021, with routinely identified genotypes being G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] and, to a smaller extent, G12P[8], with their relative dominance and prevalence varying from year to year. Consistent with EuroRotaNet data, our analysis demonstrates high genotype diversity, with lack of dominance by a particular genotype over all time-periods. Our meta-analysis reveals two uncommon genotypes, G3P[9] and G2P[6], in Poland and Iraq, respectively. However, these findings were derived from small sample sizes and should be interpreted cautiously (68 samples in Poland and 98 samples in Iraq). Of note, G9P[4] has also been identified by EuroRotaNet,¹⁰⁹ since the inception of the network (from 2006–2007 season to 2020–2021), its overall prevalence has been 1%.

This is important for rotavirus vaccination policy as it suggests that vaccination programs have had limited or no impact on the prevalence of uncommon strains from the pre-vaccination period. Additionally, to date, limited to no evidence of vaccine induced selective pressure has been found, with a recent review noting a, potentially transient, increased prevalence of G2P[4] in post-introduction scenarios.⁵ The findings echo those of an earlier systematic review, which did not find a consistent pattern indicative of vaccine related selective prevention, while indicating the need

to monitor the increased detection rate of G2P[4] genotype in some countries following RV1 vaccination.⁶ Of note, rotavirus vaccines have long been observed to possess cross-protective effects, with RV1 being suggested to be marginally less effective against fully heterotypic G2P[4].^{6,110–112}

G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and G12P[8] have frequently been identified worldwide.⁵ Of note, strains uncommon in Europe and the Middle East have been identified elsewhere. Data from 2001 to 2017 in Latin America show G9P[4] was identified in Colombia with a prevalence of ~15%, while G1P[4] was identified in Nicaragua with a prevalence of 13%;¹¹³ in Africa, G2P[6] (4.2%) and G3P[6] (3.7%) were identified Ethiopia, Zambia and Zimbabwe through a study across Eastern and Southern Africa from 2010 to 2015;¹¹⁴ while in Asia G12P[6] was identified in various surveillance studies from 2001 to 2021, including Bangladesh (no prevalence specified), Nepal (41%–45%) and India (30%), respectively.^{115,116}

Our analysis is limited by the uneven representation of countries across different timeframes and variation in the number of samples per region and time period. Some countries, such as the Russian Federation, Estonia, Finland, Ireland, and France are consistently represented, allowing for more comprehensive temporal analyses. In contrast, other countries appear only in certain periods, making trend analyses challenging.

Additionally, this study included any country regardless of vaccination introduction or uptake. Our analysis did not differentiate between countries where vaccines were available through national immunization plans or only through the private market and did not include the type of vaccine available in each country. In 2016, it was reported that 17 countries in Europe had introduced the universal rotavirus vaccines and 11 countries in the Eastern Mediterranean Region, with the vaccine type varying across countries.¹¹⁷ In many studies, where vaccination was only available through the private market, vaccination uptake rates were below 10%.^{25,42,72,74,76,78,83,118,119} By contrast, in countries with vaccination available through national immunization plans, multiple studies reported coverage levels above 90%.^{45–47,79} We did not analyze how varying coverage rates impacted rotavirus genotype circulation. However, the results from the current study can be compared with genotype prevalence in the pre-licensure data.^{5,120} As mentioned, results are consistent with those reported by EuroRotaNet, and suggest that, while the relative prevalence of genotypes varies in any given year (either during the pre and post licensure area), no new genotypes emerged in the post-licensure era.

Lastly, this study did not include sub-group analyses of genotype prevalence among specific age groups due to considerable variation of reporting in the included studies. Previous studies have shown genotype diversity was higher in older age groups¹²¹ and it is possible that we may be reporting results that apply to specific age-groups in some countries. Of note, EuroRotanet results are aggregated by country, regardless of age-group.

Finally, we did not include changes in the “DS-1-like” or “Wa-like” genotype constellation of the strains as that

information is not widely reported. However, a recent study in Belgium has noted an increase in G3P[8] (traditionally associated with a “Wa-like” constellation) with a DS-1-like constellation post-vaccine introduction.¹²² Such changes warrant further consideration in future studies.

Going forward, rotavirus genotype surveillance studies would be complemented by reporting comprehensive information on genotype constellations, and genetic diversity of rotavirus in vaccinated and non-vaccinated individuals over time.

Conclusion

Results show high variability among dominant genotypes in Europe and the Middle East in the post-licensure period, with G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] and G12P[8] being the most commonly identified genotypes. Consistent with EuroRotaNet data, there was high temporal and regional variability, with dominant genotypes varying by period and country, even among neighboring countries.

Disclosure statement

SO and CC are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and shareholders of Merck & Co., Inc., Rahway, NJ, USA, a manufacturer of RotaTeq®, a rotavirus vaccine. Triangulate Health Ltd (that employed MB, ALC, CH, TJ, HS and funded KF) received funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA to conduct the analysis. DH has received consulting fees from Merck & Co., Inc., Rahway, NJ, USA, and institutional grants from Seqirus UK Ltd, Merck & Co., Inc., Rahway, NJ, USA, and GlaxoSmithKline Biologicals. JM has received consulting fees from GlaxoSmithKline and Merck & Co., Inc., Rahway, NJ, USA.

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