HHS Public Access

Author manuscript

Pediatr Infect Dis J. Author manuscript; available in PMC 2022 September 26.

Published in final edited form as:

Pediatr Infect Dis J. 2022 September 01; 41(9): 759–763. doi:10.1097/INF.0000000000003598.

Major changes in spatiotemporal trends of US rotavirus laboratory detections after rotavirus vaccine introduction -- 2009-2021

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Keywords

rotavirus; rotavirus vaccine; seasonality

Introduction

Since oral rotavirus vaccines became available in the United States (US) in 2006, there has been a >90% decline in laboratory detections of rotavirus and an 80% reduction in hospitalizations and emergency department visits due to rotavirus among children <5 years old (1, 2). Two rotavirus vaccines are currently recommended for infants <8 months old in the United States: 2-dose Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and 3-dose RotaTeq (Merck & Co., West Point, PA, USA) (2). Despite tremendous positive impact, US rotavirus vaccine coverage has lagged behind other vaccines recommended for infants; nationally, among children born in 2017 and 2018, full 2- or 3-dose series rotavirus vaccine coverage was 76% versus 94% for the 3-dose primary DTaP (diphtheria-tetanus-pertussis) series(3).

In addition to the impact on clinical outcomes, other notable changes to rotavirus disease seasonality following rotavirus vaccine introduction have been observed. Shortly after rotavirus vaccine introduction, a pattern of alternating years of high and low rotavirus activity emerged and has been well-documented in several data sources (1, 4–6). This biennial trend has been attributed to suboptimal rotavirus vaccine coverage, resulting in an accumulation of children who are susceptible to rotavirus infection (7). Nationally, recent seasons of high rotavirus activity during the winter and spring have been shorter and started later compared to the pre-vaccine period; the number of weeks during which >10% of rotavirus stool tests were positive dropped from 26 in the pre-vaccine era to 10 in 2016-2017 and started about 4 weeks later (1).

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Conflicts of interest: The authors indicate that they have no conflicts of interest relevant to this article to disclose.

Finally, throughout the 15 years before vaccine introduction, annual US rotavirus activity showed a consistent spatiotemporal pattern, starting in the Southwest in the fall and moving across the country ending with peak activity in the Northeast in spring (8, 9). Several hypotheses explaining these regional differences in the onset of the rotavirus season prior to vaccine introduction were considered, including temperature and humidity patterns, migration of strains introduced in the Southwest, and regional differences in birth rates (9, 10). Spatiotemporal trends from the two surveillance years following rotavirus vaccine introduction did not follow the pre-vaccine era pattern (11). However, these trends have not been revisited since 2009 when national rotavirus vaccine coverage was estimated to be 43% and the biennial trend was not fully established (1, 10–12).

In this analysis, we modeled spatiotemporal trends in rotavirus laboratory detections reported to the National Respiratory and Enteric Virus Surveillance System (NREVSS) from 2009-2021, compared emerging trends to the pre-vaccine era, and considered possible factors influencing observed patterns.

Methods

We used data from NREVSS, a national passive laboratory surveillance system (13), during 12 consecutive July to June surveillance years from 2009-2021. Participating laboratories report the aggregated weekly number of total rotavirus tests performed among people of any age and the total number of rotavirus positive tests, by laboratory diagnostic method. During each surveillance year, laboratories in the 48 contiguous states reporting ≥1 enzyme immunoassay (EIA) or polymerase chain reaction (PCR) test per week during ≥26 weeks, totaling ≥100 tests in a surveillance year, were eligible to be in that surveillance year's spatiotemporal analysis. EIA and PCR tests were combined for this analysis as they generally followed similar patterns in a previous NREVSS analysis (14); however, laboratories reporting PCR tests were limited to those from pediatric hospitals to reduce statistical noise due to multi-pathogen panel tests not ordered for suspected rotavirus. While EIA is likely to be ordered for patients with suspected rotavirus, PCR tests might be more broadly used for acute gastroenteritis infections and so less specific to suspect rotavirus infections. As multipathogen assays which test for rotavirus have been more widely adopted, reporting of PCR tests has increased in NREVSS.

We determined the national duration of the rotavirus season from laboratories meeting our inclusion criteria during each surveillance year using a 3-week moving average of the percent positivity and a 10% positivity threshold to match previous definitions of rotavirus seasons (1). We limited the spatiotemporal analysis to surveillance years with ≥2 consecutive weeks of ≥10% rotavirus positivity; surveillance years that did not meet this definition were considered not to have a season of elevated rotavirus activity and thus we would not expect organized patterns of rotavirus detections. For all surveillance years, we calculated the national 7-week moving average of percent positivity and of the aggregated number of rotavirus tests and rotavirus positive tests. The national peak week for each surveillance year was defined as the week with the highest 7-week moving average of the absolute number of aggregated rotavirus positive tests; this was previously used to define peak week in geospatial NREVSS rotavirus analyses (9, 11).

For laboratories meeting the inclusion criteria during surveillance years with ≥2 consecutive weeks of ≥10% rotavirus positivity, we determined each laboratory's peak week during the national rotavirus season, as defined above. Like national peak week, laboratory peak week was the week with the highest 7-week moving average of the absolute number of rotavirus positive tests. We excluded any laboratory for which the highest 7-week moving average was ≤0.15 (i.e., there was only 1 positive test during the 7-week period). When >1 week had the highest rotavirus positive test moving average, the 7-week moving average of percent positivity was used to break the tie. We then input peak week as a continuous variable and the geospatial coordinates of each laboratory into a spherical variogram model for Kriging spatial interpolation to determine patterns of peak week across the continental United States.

To understand factors that may influence spatiotemporal trends in rotavirus activity, we included 2 additional data sources: birth rate by state and year from the Centers for Disease Control and Prevention (CDC) WONDER online database (15) and the 2010-2019 National Immunization Survey-Child (NIS-C) state-level rotavirus coverage data (16, 17). We downloaded birth rate data and calculated the average birth rate over the 10-year period from 2010-2019 by state. For NIS-C data, we downloaded each year's dataset and used the provided sampling weights to calculate the weighted percent of children 19-35 months who had completed the rotavirus vaccine series. We then averaged state-level rotavirus vaccine coverage across the 10-year period. The 33rd and 66th percentile were calculated from these averages for both birth rate and rotavirus vaccine coverage and states categorized by the 9 possible combinations of high, medium, and low rotavirus vaccine coverage and high, medium, and low birth rate. A state-level, bivariate choropleth map was created from these 9 combinations. We also calculated a composite of the average rotavirus vaccine coverage and average birth rate as (1-coverage)*birth rate. For each season, we calculated a Pearson correlation coefficient between this continuous composite and the state-level week of peak rotavirus activity.

All analyses were performed using SAS v.9.4 and R v.3.6.1.

Results

Across both high and low rotavirus activity surveillance years, there was an overall decline over time in the number of laboratories that met the laboratory inclusion criteria (Table). During 5 surveillance years (2010-2011, 2012-2013, 2014-2015, 2016-2017, and 2018-2019), there were at least 2 consecutive weeks where the percent rotavirus positivity was >10% and therefore they were included in the geospatial analysis. During these 5 years, the number of rotavirus positive tests declined from approximately 200 in 2010-2011 and 2012-2013 to 99 in 2018-2019; percent positivity during the peak week also declined from 23% in 2010-2011 and 27% in 2012-2013 to 13% in 2018-2019. Season duration also appeared to be shortening during the 5 seasons of high rotavirus activity, although the national peak week dates were in March most seasons. The total number of rotavirus tests followed the biennial trend through 2014, however in the subsequent seasons, the number of tests was relatively consistent and even may have been increasing prior to the COVID-19 pandemic beginning in 2020.

Results from the Kriging spatial interpolation during the 5 high rotavirus activity seasons are shown in Figure 1. During all 5 national high rotavirus activity seasons, the earliest peak week occurred in Arkansas, Oklahoma and the western part of the Gulf coast. During certain seasons, the Midwest and Mountain West regions also had an early peak in rotavirus activity. Across these 5 seasons, there was no clear pattern for the most delayed peak week, although the Northeast, Florida, and parts of the Southwest each had a late peak week relative to the rest of the country during >1 seasons.

The average birth rate from 2010-2019 ranged from 9.26 live births per 1,000 women in New Hampshire to 16.88 live births per 1,000 women in Utah. The birth rate declined in all states except North Dakota during this 10-year period. The average percent of children 19-35 months old with a complete rotavirus vaccine series from 2010-2019 ranged from 63% in Oklahoma to 84% in Rhode Island. Coverage increased in all states during this 10-year period. Arkansas, Louisiana, Indiana, Mississippi, Oklahoma, South Dakota and Wyoming, shown in the lightest grey in Figure 2, were in the lowest rotavirus vaccine coverage tertile and the highest birth rate tertile. This indicates these states may have larger cohorts of rotavirus susceptible children than other states. Connecticut, Massachusetts, New Hampshire, Pennsylvania, Rhode Island, and Wisconsin, shown in the darkest grey, were in the highest rotavirus vaccine coverage tertile and the lowest birth rate tertile. This indicates these states may have smaller cohorts of potentially rotavirus susceptible children than other states. The correlation coefficient between state-level peak week and the calculated average coverage and average birth rate composite was −0.25 in the 2010-2011 season, −0.45 in 2012-2013, −0.57 in 2014-2015, −0.28 in 2016-2017, and −0.05 in 2018-2019 (Figure 3). There was an inverse relationship between state-level peak week and the average rotavirus vaccine coverage and average birth rate composite during 4 seasons (2010-2011, 2012-2013, 2014-2015, and 2016-2017), with an earlier peak week in states with a higher composite score. No such relationship was seen in the 2018-2019 season.

Discussion

In this analysis, we found changes to spatial patterns in the peak week of rotavirus activity across the US following rotavirus vaccine introduction, consistent with initial post-vaccination data (11). Prior to rotavirus vaccine introduction, the earliest peak week occurred in the Southwest (8, 9, 11), however our findings show this has shifted to Arkansas, Oklahoma, and the western Gulf Coast area. Unlike the pre-vaccine era, we did not find states or a region that consistently had the latest week of rotavirus peak activity during the national season. In analyses during the pre-vaccine era, the distinct annual pattern was hypothesized to be due to meteorological factors, however the shift seen in this analysis suggests temperature and humidity may not be driving the onset of peak rotavirus activity. Our findings that show a biennial trend in high rotavirus activity are consistent with other data published since rotavirus vaccine introduction. Our findings are also consistent in showing low rotavirus disease activity during the first 2 years of the COVID-19 pandemic (14).

To understand the shift in earliest peak week eastward, we calculated a composite of birth rate and rotavirus vaccination coverage and found a concentration of states with both the

average lowest coverage and highest birth rate also show earliest peak rotavirus activity. This moderate correlation was confirmed during all seasons except 2018-2019, when there were fewer contributing laboratories and less variation in peak week. Before rotavirus vaccine introduction, there were several potential hypotheses for regional differences in the onset of the rotavirus season before vaccine introduction, including birth rate (10). The observed patterns found in this analysis support the birth rate hypothesis as the driver of seasonal patterns and is consistent with other findings showing suboptimal coverage as a cause of the biennial trend. Further analyses are needed to better understand how birth rate and rotavirus vaccination coverage may be co-contributing to rotavirus seasonal trends and how these trends may evolve as coverage increases. These findings affirm that increasing rotavirus vaccine coverage is key to reducing disease burden.

This analysis has several limitations. First, we combined EIA and PCR laboratory tests despite not being from the same source populations, as PCR tests were limited to pediatric hospitals, and there are differences in sensitivity between the tests. No information about age, healthcare setting, or reason for testing is available in NREVSS. As rotavirus primarily effects children <5 years old, combining EIA and PCR results for rotavirus detection was the best option to have an adequate sample size for this analysis. However, combining the results from these two test types may have affected the magnitude of rotavirus positivity and thus also influenced the timing of the start of the rotavirus season and the peak week of rotavirus activity compared to other previous analyses using EIA results only. In an earlier NREVSS analysis, EIA and PCR tests from pediatric hospitals were found to have similar magnitude and generally similar peak week (14). Second, the number of included laboratories decreased over time and the geographic sparseness of laboratories, particularly in the Mountain West region, may have obscured additional nuance. The declining number of laboratories contributing in NREVSS has been previously noted (1, 14) and may be attributed to declines in testing due to lower disease burden and changing testing practices from EIA to PCR. As PCR tests became more common during the later study period, this may explain why the overall number of tests was consistent while the number of contributing labs declined. Third, our comparisons with birth rate and coverage are ecological and states may not have homogeneous birth rates and vaccine coverage. Similarly, we were unable to consider factors like birth order or childcare attendance, as no individual level data were available. Finally, our analysis ended with the 2018-2019 season. As rotavirus detections were depressed during the COVID-19 pandemic (14), monitoring these trends after the pandemic will continue to be important.

This analysis agrees with earlier studies that found changes in rotavirus seasonality and spatiotemporal trends in the US since rotavirus vaccine introduction. The concordance of the earliest seasonal rotavirus activity with high birth rate and low vaccine coverage likely means a more rapid accumulation of susceptible children, driving seasonality, and reaffirms that universally high, timely rotavirus vaccine coverage is a key tool in reducing rotavirus disease burden.

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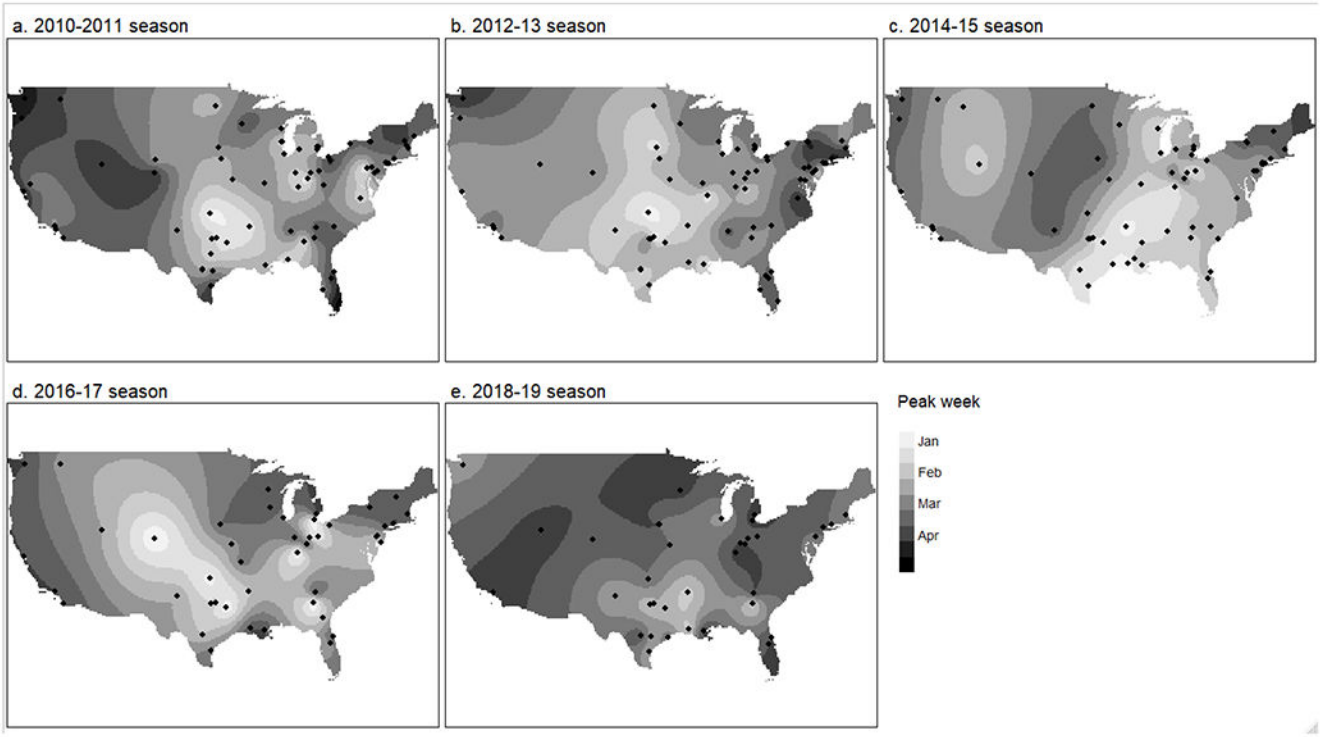

Figure 1.

Peak week of rotavirus activity by surveillance year, NREVSS, United States, 2010-2019. The black dots indicate the locations of participating laboratories.

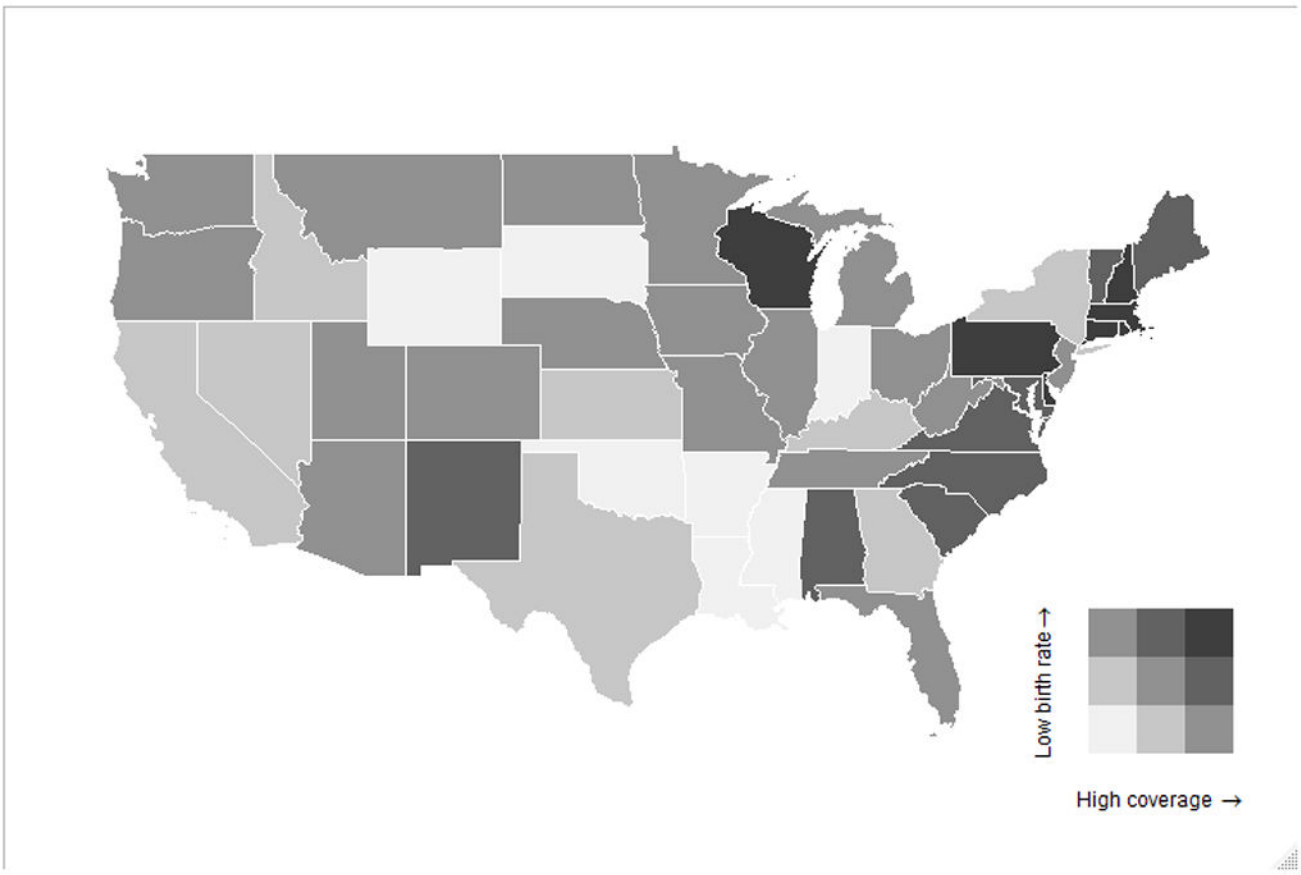

Figure 2.
Average birth rate and rotavirus vaccine coverage by state, United States, 2010-2019

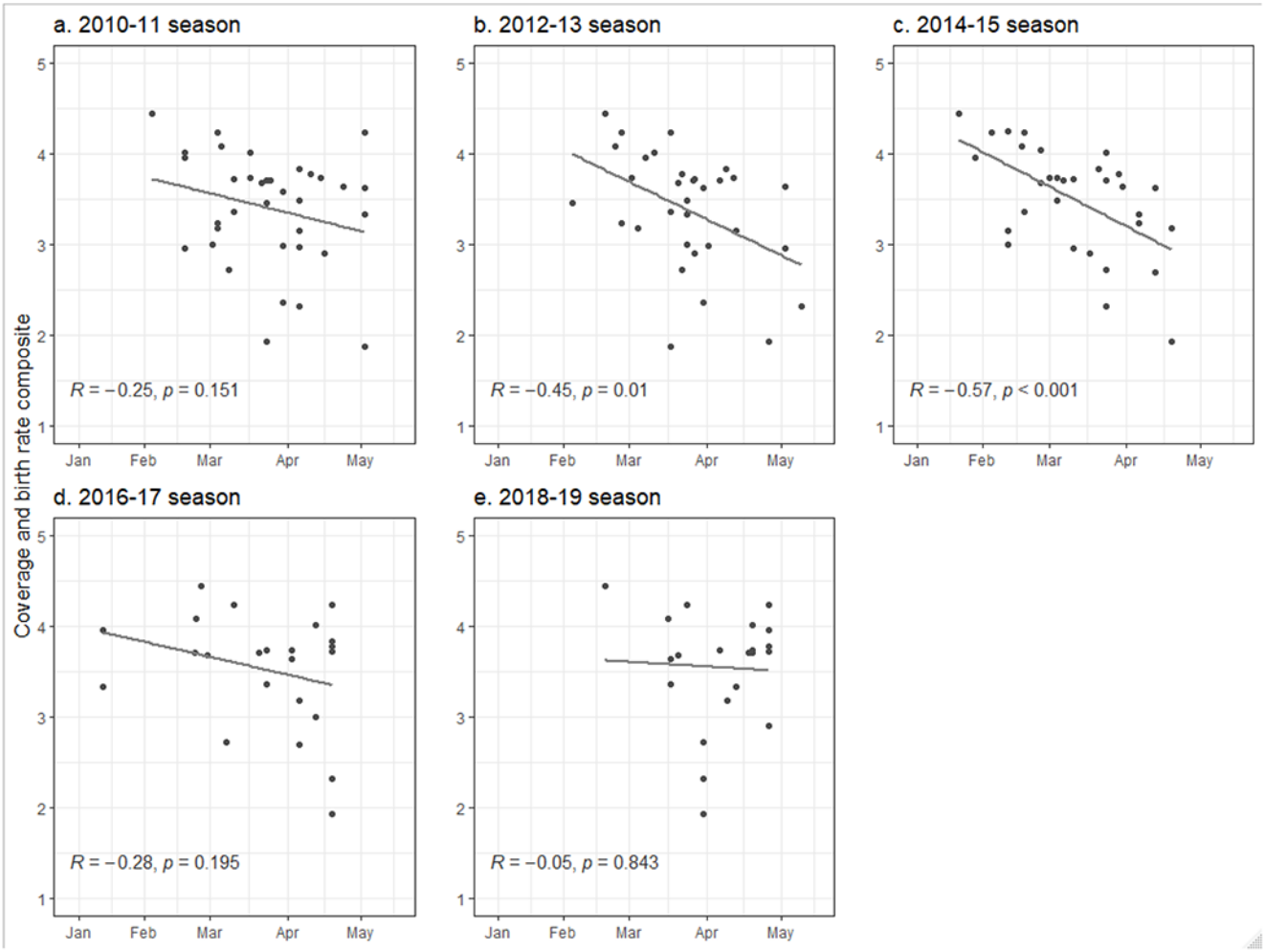

Figure 3.

Correlation between state-level peak week and composite of the average rotavirus vaccine coverage and average birth rate by season. Each dot represents an individual laboratory.

Table 1.

Surveillance year selection for the geospatial analysis and rotavirus peak activity week among seasonal continuously reporting laboratories[1] to the National Respiratory and Enteric Surveillance System (NREVSS), United States, 2009-2021.

			Season >10% positivity[2]		Peak week			
Season	Laboratories contributing rotavirus testing data to NREVSS	Number of laboratories included in analysis[1]	First week	Last week	Peak week[3]	% positive[4]	Rotavirus positive tests[4]	Total rotavirus tests[4]
2009-10	198	75	-	-	4/26/2010	10%	54	603
2010-11	161	78	1/17/2011	5/23/2011	3/28/2011	23%	193	826
2011-12	157	76	-	-	5/7/2012	7%	33	521
2012-13	140	76	1/14/2013	5/6/2013	3/18/2013	27%	217	885
2013-14	149	55	-	-	5/5/2014	9%	36	433
2014-15	120	63	1/5/2015	4/13/2015	2/16/2015	21%	133	658
2015-16	118	52	-	-	4/25/2016	4%	21	518
2016-17	136	50	1/9/2017	4/17/2017	3/6/2017	14%	91	609
2017-18	113	43	-	-	5/7/2018	8%	55	727
2018-19	81	39	2/11/2019	4/22/2019	3/25/2019	13%	99	786
2019-20	111	37	-	-	2/24/2020	3%	25	830
2020-21	87	25	-	-	4/19/2021	2%	16	582

[1] Continuously reporting laboratories submitted at least 1 enzyme immunoassay (EIA) or polymerase chain reaction (PCR) test for 26 weeks totaling at least 100 tests per surveillance year

[2] 3- week moving average

[3] Epidemiologic week start date

[4] 7- week moving average