Trends in Laboratory Rotavirus Detection: 2003 to 2014

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abstract

OBJECTIVES: We assessed the impact of rotavirus vaccination at national and state levels by evaluating the change in rotavirus antigen detection after vaccination licensure. We examined herd immunity in an unlikely vaccinated cohort and waning immunity with aging in a likely vaccinated cohort. We proposed a new approach to estimate the length of season by contrasting with what is recently reported by the Centers for Disease Control and Prevention.

METHODS: We analyzed 11-year results of rotavirus testing (n = 276 342) conducted at Quest Diagnostics, a national clinical reference laboratory, spanning from September 2003 to August 2014. An enzyme immunoassay was used to test children's stool specimens for the presence of rotavirus antigen; results were reported as not detected or detected.

RESULTS: Nationally, there was a significant reduction in the number of positive results (82.4%) and positivity rate (73.3%) after vaccination availability. The reductions were seen in all major states, although with geographic variability. The declining positivity rate in unlikely vaccinated children suggests herd immunity. Among those who were likely vaccinated, the positivity rate was higher in older children, indicating potential waning immunity with aging. Seasonal outbreaks continued in the postvaccine period, with peaks in alternating years. Seasons were longer in the postvaccine period than the prevaccine period.

CONCLUSIONS: Our findings show a marked reduction in rotavirus detection throughout the nation after vaccine licensure, consistent with herd immunity. Postvaccine effectiveness may wane with aging. Seasons appear to be longer in the postvaccine period.

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Dr Kaufman conceptualized and designed the study and drafted the initial manuscript; Ms Chen carried out the analyses and reviewed and revised the manuscript; and both authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Declines in rotavirus activity followed vaccine introduction. Some US studies also reported herd immunity. A publication from the Centers for Disease Control and Prevention described a biennial pattern of rotavirus activity in the postvaccine era.

WHAT THIS STUDY ADDS: This study validates previously reported key findings with more laboratory-confirmed results over an extensive period. It additionally confirms observations by stratifying results based on gender and state. This study proposes a new approach, more meaningful to medical practitioners, estimating season length.

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Rotavirus is the most common cause of severe, dehydrating gastroenteritis in infants and young children worldwide. In the United States, before the availability of efficacious vaccines, rotavirus infections caused ~410 000 physician visits, 205 000 to 270 000 emergency department visits, and 55 000 to 70 000 hospitalizations annually.[1] Two oral rotavirus vaccines have been licensed and are recommended by the Advisory Committee on Immunization Practices (ACIP) for routine use in infants in the United States; RotaTeq (RV5) licensed in February 2006 and included in the August 2006 ACIP recommendations and Rotarix (RV1) licensed in April 2008 and added to ACIP recommendations in June 2008.[2,3] The vaccines were found to be 70% to 84% effective against rotavirus-associated emergency department visits and hospitalizations combined.[4]

To evaluate the long-term impact of vaccination, we analyzed 276 342 results of rotavirus antigen detection testing using enzyme immunoassay, conducted at a US national clinical reference laboratory over an 11-year period (September 2003 through August 2014). We compared our observations with those recently reported by the Centers for Disease Control and Prevention (CDC).[5]

METHODS

Quest Diagnostics has ~150 million patient encounters annually with individuals from every state across the United States and Washington, DC. This study is part of Quest Diagnostics Health Trends, which is a series of reports and studies designed to identify and track disease and wellness trends to inform patients, healthcare professionals, and policy makers about the current status of the nation's health based on the deidentified results. For this rotavirus study, we included all children <10 years with rotavirus antigen detection results from September 2003 through August 2014, from all 50 states in the United States and Washington, DC. Stool specimens of children were tested for the presence of rotavirus antigen using an enzyme immunoassay (Meridian Bioscience, Inc, Cincinnati, OH) at Quest Diagnostics laboratories throughout the study period. The results were reported as rotavirus antigen detected, not detected, or equivocal. All analyses in the study were based on tested specimens with a definitive detected or not detected result. Results with missing gender and state data were excluded from specific analyses that required those elements. The study was deemed exempt by Western Institutional Review Board (Puyallup, WA).

A rotavirus reporting year was defined as September through August, because the lowest positivity generally occurred in August and September of each year. The prevaccine period was defined as the 3 years before vaccine licensure (September 2003 through August 2006), the transition period as the subsequent 1 year (September 2006 through August 2007), and the postvaccine period as the next 7 years (September 2007 through August 2014).

The length of each rotavirus season in a reporting year was estimated by 2 approaches. The first is based on the approach used by the CDC[5]: the start of each season was defined as the first week of the first 2 consecutive weeks in which the positivity rate was ≥10%, and the end of each season was defined as the second week of the last 2 consecutive weeks in which the positivity rate was ≥10%. The second approach is based on the distribution of the number of positive rotavirus antigen detection results, over weeks: the central 68% (representing the proportion within ~1 SD of the median) and central 80% (representing the proportion between the 10th percentile and 90th percentile, ~1.28 SDs from the median) of positive test results. The definition of the central 68% and central 80% describes a window of time when the majority of positive test results occurs within each season. The second approach was only applied to the reporting years with at least 10% positivity by using the CDC's definition to be able to compare 2 approaches. "Weeks" used in denoting rotavirus seasons are epidemiologic (EPI) weeks as described by the CDC.[6]

The patients were categorized into 3 cohorts based on presumed vaccine status according to age and date of initial vaccine licensure. The patients in the "unlikely vaccinated" group were born on or before July 31, 2006 (ie, before the ACIP recommendation for vaccination); the "possibly vaccinated" group was born between August 1, 2006 and August 31, 2007; and the "likely vaccinated" group was born on or after September 1, 2007. We only compared the unlikely and likely vaccinated patients, because the possibly vaccinated group was born in the first year after licensure of vaccine when there was extensive variation in adoption of the new vaccine. Available data also suggest that the proportion of children receiving vaccination outside the recommended age windows was higher during the first few months after vaccination availability than after mid-2007, because of the complexity of the age recommendations.[7]

For age-based analyses, children were grouped in 1-year intervals up to age 4 years. Children 5 through 9 years of age, inclusive, were combined as 1 age group because this age group had fewer patients at each year of age than younger patients and, more importantly, age 5 years is a natural cutoff in rotavirus studies.

For state-based analyses, we only focused on the rotavirus antigen detection results in the 7 states with the highest numbers of positive

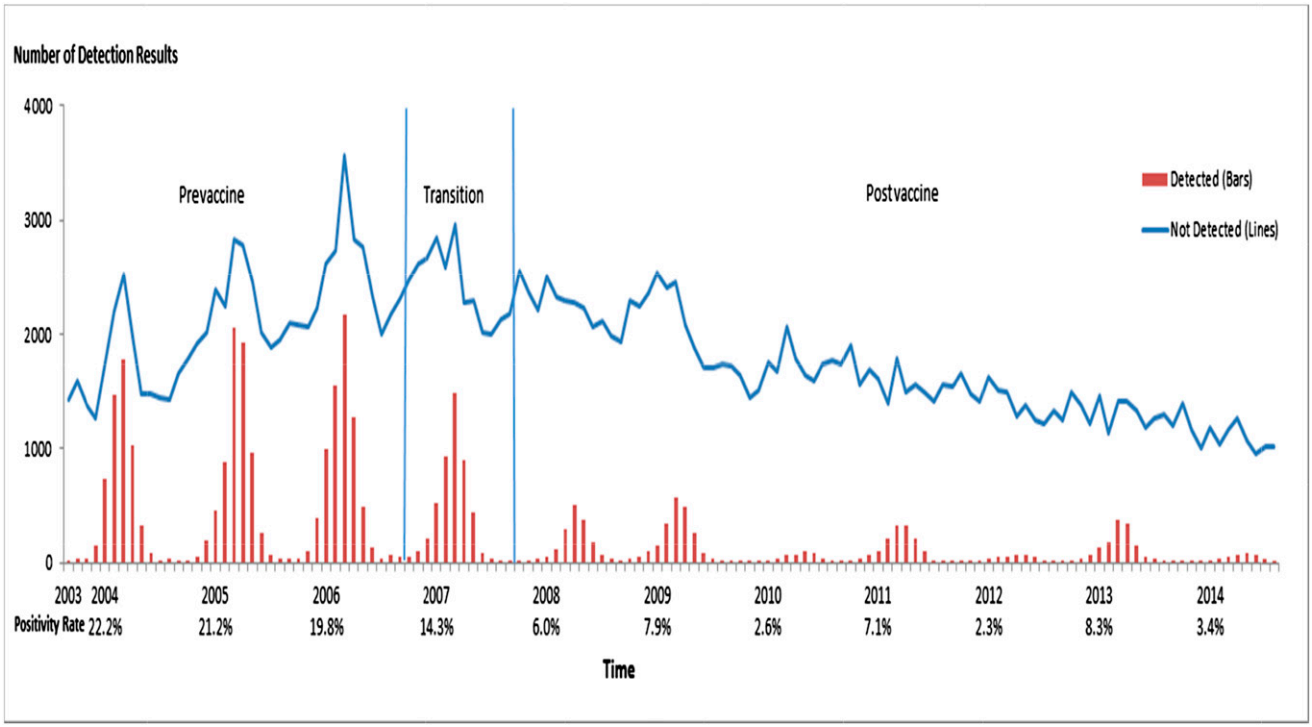

FIGURE 1
Number and rate of rotavirus antigen detection results over the 11-year study period among all children, September 2003 through August 2014.

results in the prevaccine period (minimum of 1000 over the 3-year period): Arizona, California, Florida, Georgia, New York, Pennsylvania, and Texas. These 7 states accounted for over half of all positive test results in the prevaccine period.

Statistical significance of comparisons was tested by using Pearson's χ^2 test to assess the difference between proportions. Analyses were performed in SAS 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Over the 11-year period, 276 949 specimens were submitted for rotavirus antigen detection. Of these specimens, 276 342 (99.8%) had a definitive result of detected or not detected whereas 607 were reported as equivocal. Of all of the specimens with a definitive result, 3966 (1.4%) were missing gender information and 1217 (0.4%) were missing geographic (state) information. Boys consistently comprised 56% of the population with gender data for each of the 3 time periods. During the September 2003 through August 2006 (prevaccine) period, Quest Diagnostics had overall growth in testing volume, and it is unclear why rotavirus antigen detection testing grew faster. In the 2008 through 2014 period, overall testing volume was relatively stable.

In the prevaccine period, the laboratory performed an average of 31 800 tests for rotavirus antigen detection annually, of which 21.0% (95% confidence interval [CI]: 20.7%–21.2%, n = 6662) were positive. These numbers decreased in the postvaccine period, when an average of 20 981 annual tests were performed and 5.6% (95% CI: 5.5%–5.7%, n = 1175) had positive results (Fig 1). This represents an 82.4% reduction in the total number of positive results and a 73.3% reduction in the positivity rate (P < .001). During the transition period, the positivity rate for rotavirus antigen detection was 14.3% (n = 4874). This represents a 26.8% reduction in the positive number and a 31.9% reduction in the positivity rate compared with the prevaccine period (P < .001). The positivity rate during each of the 3 periods was virtually identical for boys and girls: 21.1% for boys and 20.9% for girls during the prevaccine period, 9.8% for boys and 9.6% for girls in the transition period, and 4.9% for boys and 4.6% for girls in the postvaccine period.

Within the 3 years of the prevaccine period, the overall positivity rate also declined slightly nationwide, from 22.2% to 21.1% then to 19.8% (Fig 1). But this declining trend was variable among states. Within the 7 years of the postvaccine period, our data showed a bi-year peak, with the positivity rate alternating between 2.3% to 6.0% in the even years and 7.1% to 8.3% in the odd years (Fig 1). A similar pattern was observed in each of the 7 states except for Arizona. Arizona's alternating pattern started in the second year of the

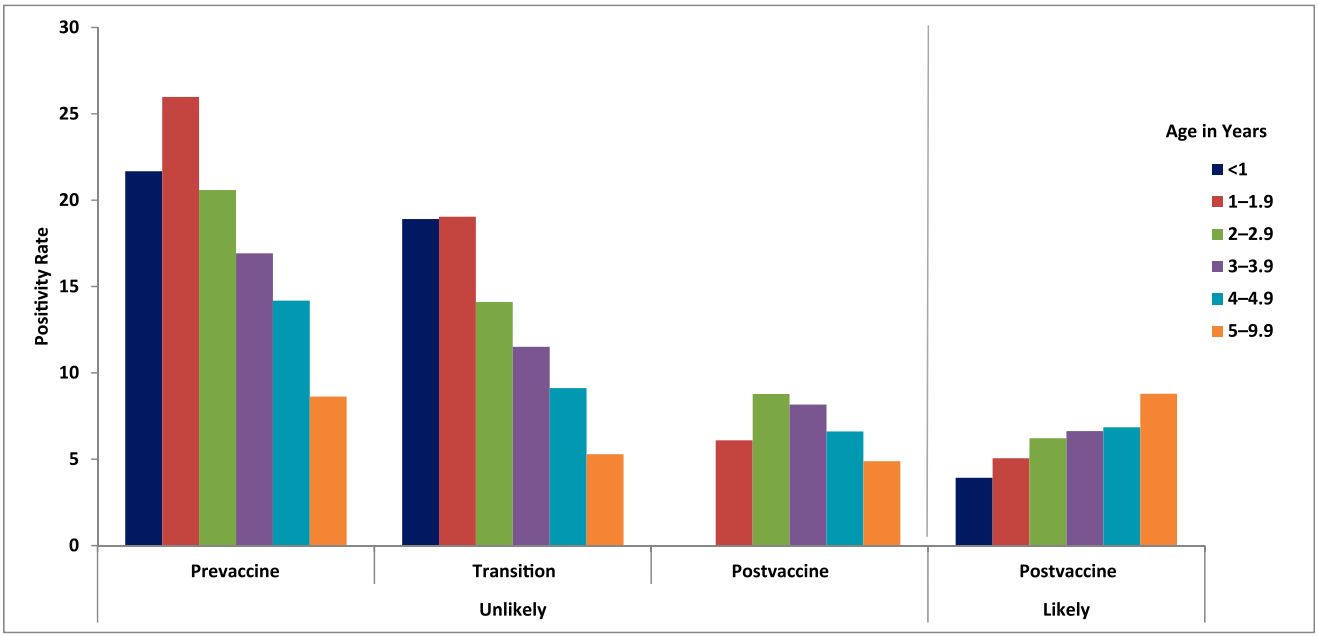

FIGURE 2

Positivity rate of rotavirus antigen detection results by age and vaccine status (unlikely and likely), September 2003 through August 2014. By definition, for children in the "Unlikely Vaccinated" group, there are no data in age group <1 year in the postvaccine period. By definition, for children in the "Likely Vaccinated" group, there are no data in the prevaccine and transition periods.

postvaccine period, 1 year later than the other 6 states, and its peaks were higher than the other states across the postvaccine period.

We stratified patients by presumed vaccination status, based on the patient's age in regard to the date of initial vaccine licensure. In children who were "unlikely vaccinated" (born on or before July 31, 2006), the overall positivity rate in rotavirus antigen detection was 21.0% (95% CI: 20.7%–21.2%) in the prevaccine period and dropped to 6.3% (95% CI: 6.0%–6.5%) in the postvaccine period ($P < .001$). The declining positivity rates were observed in all age groups (by definition there are no children <1 year old in the postvaccine cohort) (Fig 2). In the prevaccine and transition periods, there was a linear decline starting at 2.0 years of age and continuing through the oldest age group. In the postvaccine period, the decline in positivity was observed starting in children ≥3.0 years (Fig 2). Among children who were "likely vaccinated" (born on or after September 1, 2007), the trend was largely reversed with the highest positivity rate in children 5.0 to 9.9 years old (by definition there are no children in the prevaccine and transition periods) (Fig 2). When comparing 2 groups in the postvaccine period, for children ≤3.0 years of age, the "unlikely vaccinated" cohort was more likely to have positive rotavirus test results than the "likely vaccinated" cohort; for children ≥4.0 years, the positivity rate was higher in the likely vaccinated population than among children unlikely to have been vaccinated (Fig 2).

The length of season was estimated using 2 different approaches: (1) the CDC definition (at least 10% positivity), (2) the central 68% and 80% of positive test results (Table 1). Using the CDC definition of at least 10% positivity, the data from this study paralleled the CDC observations that seasons were shorter after vaccine implementation; however, seasons were consistently 2 to 3 weeks shorter in our data than in the CDC report for both the prevaccine period and the 3 peak years after vaccine implementation.[5] In contrast, using the definition of the central proportion of positive rotavirus antigen detection results over EPI weeks (both 68% and 80%), season length tended to increase after vaccine licensure (Table 1). Based on the central 68% and 80% proportion approach, the average length was 14.7 and 20 weeks, respectively, in the 3 peak years of the postvaccine period, compared with 11.5 and 15 weeks in the prevaccine period.

DISCUSSION

The CDC report had included 79 479 results over 14 years and did not reflect uniform coverage across the United States.[5] In contrast, our study included 276 342 rotavirus antigen detection results among children over an 11-year period, with broad representation across the nation, and reported with more detailed analysis at the state level and by gender stratification. Our study included more than twice as many children

on average per prevaccination and postvaccination reporting year. Our general observations of the impact of vaccination are consistent with those reported by the CDC except regarding the length of the rotavirus seasons in the prevaccination and postvaccination periods.

Our findings suggest that vaccination has been effective at reducing rotavirus infections among infants and children in the United States, with a 73.3% decrease in rotavirus antigen positivity rate in the postvaccine period. Similarly, the CDC reported a decline of 57.8% to 89.9% in the 7 postvaccine years compared with the prevaccine period.[5] The decline in overall volume of rotavirus antigen detection testing may be because of the impact of fewer children being infected, and more children protected by herd immunity.[8,9] The dramatic decline in rotavirus antigen detection is likely a key contribution to a reported decline in healthcare use for diarrhea among children in the United States.[10] The overall reduction of 73.3% is approximately what is expected based on the vaccine coverage rate (69% of infants with at least 1 vaccine dose[11]).

Although this study did not directly obtain data comparing positive proportion of rotavirus antigen detection between vaccinated and unvaccinated individuals, a comparison of test results before and after vaccine availability demonstrated presumptive evidence of herd immunity among children who were too old to have been recommended for vaccination when vaccines became available. The lower positivity rates in more recent years suggest that many of these unlikely vaccinated children were protected because of a lower rate of exposure to potential sources of infection in the community. In this group, the older children tended to have an even lower positivity rate in the postvaccine period, suggesting the protection of these children is due to herd immunity and immunity secondary to viral exposure. This observation is consistent with a report that gastroenteritis hospitalizations have decreased in older children after rotavirus vaccine licensure.[12]

TABLE 1 Length of Rotavirus Season in EPI Weeks, September 2003 Through August 2014

Reporting Year	CDC (at Least 10% Positivity)[5]	Quest Diagnostics		
		At Least 10% Positivity	Central 68%	Central 80%
Prevaccine[a] (median)	26	22.5	11.5	15.0
2006–2007 (transition)	Not reported	21	13	17
2007–2008	12	12	13	18
2008–2009 (peak)	17	15	13	18
2010–2011 (peak)	18	16	16	22
2012–2013 (peak)	17	14	15	20

Peak refers to the 3 most recent peak years after vaccine licensure in terms of the CDC's approach.
[a] 2000 to 2006 for CDC's data, 2003 to 2006 for Quest Diagnostics data.

A novel observation is the rise in the positivity rate of rotavirus antigen detection in the likely vaccinated children as they aged. This pattern is the opposite of what we observed in children who were unlikely to have been vaccinated. This different pattern suggests that natural immunity may have protection in the unlikely vaccinated children as they age, but that protection wanes among children who are likely to have been vaccinated. Protection after the second season after vaccination has not been studied.[2,3] Additional study is required to confirm this observation and to understand why the positivity rate is similar among children ages 5.0 to 9.9 years in the prevaccine period who were unlikely to have been vaccinated and in the postvaccine period who were likely to have been vaccinated.

The initial decline in rotavirus detection varied among states, which may reflect differences in vaccine uptake. We speculate that the modest variation among the 7 states with the highest numbers of positive rotavirus test results during the prevaccine period may have been because of modest variation in the spread of infection based on geography. One possible explanation is that some seasonal outbreaks may be more severe in some states than in others. The decline in the positivity rate occurred over 2 years after vaccine licensure with the notable exception of Arizona, where the decrease was first noted in the third year.

Rotavirus appeared to be an equal opportunity virus, affecting both boys and girls at similar rates.

The cyclic pattern observed in the 7 reporting years of the postvaccine period is consistent with the oscillatory fluctuations reported by Anderson and Grenfell[13] for measles, pertussis, and mumps. The biennial pattern of rotavirus infection is also identical to that reported by the CDC.[5] One explanation noted by Tate et al[7] states that there may be an accumulation of susceptible children after the previous nonactive season, when rotavirus transmission is markedly decreased.

The approach employed by the CDC to define the length of season as 10% or greater positivity is flawed in design. In the CDC approach,[5] when comparing any 2 curves, one nested within the other, the curve with higher positivity rate will always, by definition, have the longer season

with a single percent criterion (10% in the CDC paper). Our study used an alternative approach, the central 68% and 80% of the proportion based on the distribution of number of positive rotavirus antigen detection cases over a rotavirus reporting year. This approach shows the length of a window when the majority of positive rotavirus detection results takes place in each reporting year, which is unaffected by the overall positivity rate of that year. By using this alternative approach, the length of each season in the postvaccine period increased rather than decreased as reported by the CDC for all peak seasons. Being cognizant of the temporal spread of the occurrence of positive tests in rotavirus peak years after vaccine licensure is more meaningful and intuitive for medical practitioners, given the common awareness of decreasing positive rotavirus cases.

Limitations of this study include lack of correlation of vaccine status to individual children and lack of aggregate regional vaccination coverage data and protection against rotavirus infection. The data are representative of children who received testing through 1 US national clinical reference laboratory. There is no information as to the clinical indications for testing, although the presumption is that all children exhibited diarrhea at the time of testing. In addition, the potential changes in physician and patient demographics and ordering over the 11-year period served by the US national clinical reference laboratory may potentially have affected our observations.

CONCLUSIONS

Rotavirus vaccination, introduced in August 2006, appears to have greatly reduced rotavirus incidence as reflected by antigen detection across the United States. The impact was equivalent for boys and girls. The data support the notion of herd immunity in children unlikely to have been vaccinated. We raise the possibility that immunity through vaccination wanes with aging. Although the postvaccination period featured alternating years of higher and lower positivity, the peak seasons have a lower positivity rate than in the prevaccination period. In contrast to the CDC report,[5] we observed that in the postvaccine period, the length of seasons was longer than in the prevaccine period.

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ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices
CDC: Centers for Disease Control and Prevention
CI: confidence interval
EPI: epidemiological

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